Totally Synthetic Steroid Hormones. VII.[1] Some (±)-8α-Estrane and (±)-13β-Alkyl-8α-gonane Derivatives

G. C. BUZBY, JR., E. CAPALDI, G. H. DOUGLAS, D. HARTLEY, D. HERBST, G. A. HUGHES, K. LEDIG, J. MCMENAMIN, T. PATTISON, HERCHEL SMITH,[2] C. R. WALK, G. R. WENDT,

Research and Development Divisions, Wyeth Laboratories, Inc., Radnor, Pennsylvania

J. SIDDALL,

Chemistry Department, Manchester University, Manchester 13, England

B. GADSBY, AND A. B. A. JANSEN

John Wyeth & Brother Ltd., Huntercombe Lane South, Taplow, Maidenhead, Berkshire, England

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A series of (±)-13β-alkyl-8α-gona-1,3,5(10)-trienes of types **4** and **5** has been totally synthesized for investigation as possible nonfeminizing, blood lipid lowering agents. The (±)-alcohols (**5**, R = CH_3 and C_2H_5; R^1 = H) have been converted to the corresponding ketones (**10**, R = CH_3 and C_2H_5; R^1 = C≡CH), required for biological evaluation. Various biological activities of these compounds are briefly described.

Reports of the considerable retention of hormonal activities by an (±)-estrone stereoisomer,[3] subsequently shown to be (±)-8α-estrone,[4] and by 8α-progesterone[5] and 8α-testosterone[5] prompted us to extend the synthetical methods described in earlier papers[6-8] to prepare a variety of related (±)-estrane and (±)-13β-alkylgonane derivatives for biological evaluation. A part of the work relating to the ring A aromatic members of our series has already appeared in the patent literature.[9]

(±)-8α-Estra-1,3,5(10)-trienes and (±)-8α-Gona-1,3,5(10)-trienes.—We have shown that the (±)-estrapentaenes (**1**, R = CH_3; R^1 = H, CH_3, and CH_3CO)[6,7] give predominantly the corresponding 8α-estratrienes (**4**)[10] by catalytic hydrogenation in ethanol over a palladium catalyst, and that the estrapentaene (**1**, R = R^1 = CH_3) and the gonapentaenes (**1**, R = C_2H_5 and *n*-C_3H_7; R^1 = CH_3) give the corresponding tetraenes of class **7** by similar hydrogenation in benzene.[6-8] Accordingly, we could assume that the palladium-catalyzed uptake of 2 moles of hydrogen by the pentaenes (**1**, R = C_2H_5; R^1 = H, CH_3, and CH_3CO) would lead to the corresponding 8α-gonatrienes. The gonatriene formulated as **4** (R = C_2H_5; R^1 = CH_3) is obtained from the ketone **1** (R = C_2H_5; R^1 = CH_3) by this process, and from its cyclic ethylene ketal **3** (R = C_2H_5; R^1 = CH_3) by catalytic hydrogenation and acid hydrolysis. Sodium borohydride converts the ketone **4** (R = R^1 = CH_3) into an alcohol (**5**, R = R^1 = CH_3) shown to be a 17β-ol from its identity with that formed by hydrogenating the tetraene **8** (R = R^1 = CH_3).[8b] The same alcohol is also produced by hydrogenating the precursor **2** (R = R^1 = CH_3) made by sodium borohydride reduction of the ketone **1** (R = R^1 = CH_3). Analogous transformations have been observed with corresponding 13-ethylgonane derivatives (see Experimental Section). The phenol **4** (R = C_2H_5; R^1 = H) is formed from the phenol **1** (R = C_2H_5; R^1 = H) by the usual catalytic hydrogenation, or from the ether **4** (R = C_2H_5; R^1 = CH_3) by demethylation in molten pyridine hydrochloride.[11] The Experimental Section describes the preparation of representative members of the series **4** and **5** having R = CH_3 and C_2H_5. Details on the whole series, including members having R = *n*-C_3H_7, *i*-C_3H_7, *n*-C_4H_9, *i*-C_5H_{11}, and *n*-$C_{16}H_{33}$, are listed in Table I.

As with the corresponding estra-1,3,5(10)-trienes,[8] elongation of the angular group produces an improvement in the ratio of blood lipid lowering: feminizing activities. The alcohols of type **5** are generally better blood lipid lowering agents than the corresponding ketones, showing considerable activity even with the branched-chain 13β-alkyl substituents. The alcohols **5** (R = CH_3 and C_2H_5; R^1 = CH_3) are outstanding members of this series; in a rat blood cholesterol depression test[12] and a mouse uterine growth test,[13] the first had 260 and 3%, respectively, and the second 500 and 3%, respectively, of the activity of estrone. An estranimetric agent with a sufficient separation of blood lipid lowering and feminizing properties would be of potential use in the treatment of atherosclerosis.[14] Recently Velluz, *et al.*,[15] have recorded further data on the feminizing activity of 8α-estrone and 8α-estradiol.

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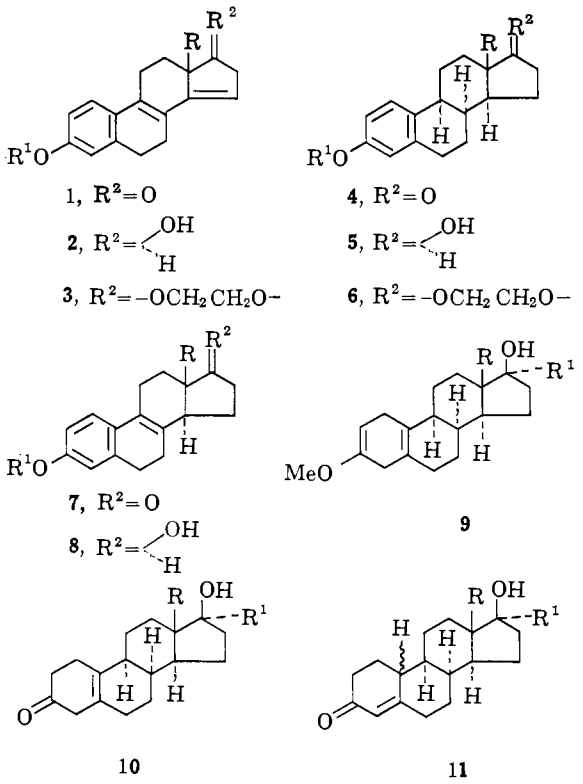

(±)-8α-Estr-5(10)-en-3-ones and (±)-13β-Ethyl-8α-gon-5(10)-en-3-ones.—The claim[5] that 8α-progesterone has one-third of the progestational activity of the parent hormone in the Clauberg test, coupled with the observed estrogenic–progestational activities[16] of 17α-ethynyl-17β-hydroxyestr-5(10)-en-3-one, made it of interest to examine the biological properties of the series **10** (R ≥ CH_3; R^1 = C≡CH). The 13-methyl and -ethyl members were prepared from the respective gonatrienols **5** (R = CH_3 and C_2H_5; R^1 = CH_3) by Birch reduction to the dienes **9** (R = CH_3 and C_2H_5; R^1 = H) followed by Oppenauer oxidation, reaction with lithium acetylide, and mild acid hydrolysis of the resulting alcohols **9** (R = CH_3 and C_2H_5; R^1 = C≡CH). Mineral acid treatment of the alcohols **10** (R = CH_3 and C_2H_5; R^1 = H and C≡CH) under conditions[8] whereby the corresponding estrenones and 13β-alkylgonenones give high yields of estr-4-en-3-ones and gon-4-en-3-ones, respectively, leads to mixtures containing, from their infrared absorption spectra, comparable amounts of the ketones of type **10** in admixture with Δ⁴-3-ketonic isomers (**11**). Similar mixtures were obtained by mineral acid treatment of the dienes **9** (R = CH_3 and C_2H_5; R^1 = H and C≡CH). Since the isomerizations of cyclohex-3-en-1-ones to cyclohex-2-en-1-ones are thermodynamically controlled,[17] the results imply that a substance of class **10** is comparable in stability with its Δ⁴-3-ketonic isomer(s). In no case have we any knowledge of the relative proportions of 10α and 10β stereoisomers in the α,β-unsaturated ketonic component, although the fact that a 10β member of the class **11** must have either ring B or C in a boat conformation (probably the former[18]) suggests that it should be less stable than its 10α counterpart. Birch, *et al.*,[19] have noted the resistance to complete conjugation under acid conditions of the double bond in Δ⁹-octal-2-one, an observation confirmed by later workers.[20]

The ketone **10** (R = CH_3; R^1 = C≡CH) has also been prepared by conversion of the alcohol **9** (R = CH_3; R^1 = H) to the corresponding 3-ethylene ketal, oxidation of the 17-hydroxyl function, and conversion of the resulting **17**-one to a 17α-ethynyl-17β-ol,[21] followed by mild acid hydrolysis.

In the Clauberg test[22] the ketones **10** (R = CH_3 and C_2H_5; R^1 = C≡CH) had 5 and 0%, respectively, of the progestational activity of progesterone. In a pituitary blockage test,[23] a **159**-μg dose of the first compound and a 236-μg dose of the second completely inhibited the compensatory hypertrophy of the remaining ovaries in hemicastrated female rats. These doses are to be compared with the similarly effective dose of 72.5 μg determined for 17β-hydroxy-17α-ethynylestr-5(10)-en-3-one.[23b]

Experimental Section

Melting points were determined in capillary tubes (Thomas–Hoover apparatus) and are uncorrected. Ultraviolet absorption spectra were determined in 95% ethanol solutions. All hydrogenations were at atmospheric pressure. Representative experiments are described for compounds of the (±)-8α-estrane and (±)-13β-ethyl-8α-gonane series. Other compounds, with further details and analyses, are given in the collective Table I. The method of preparation of any (±)-13β-alkyl-8α-gonane derivative follows upon that used for its closest 13-methyl or -ethyl analog. Where more than one preparation can apply, those used have been denoted by the appropriate prefixes (i), (ii), and (iii). The necessary starting materials for these preparations were obtained as previously described.[6-8]

(±)-13β-Ethyl-3-methoxy-8α-gona-1,3,5(10)-trien-17-one (4, R = C_2H_5; R^1 = CH_3). (i)—(±)-13-Ethyl-3-methoxygona-1,3,5(10),8,14-pentaen-17-one (80 g) was shaken with hydrogen in methanol (2.2 l.) containing 10% palladized charcoal (35 g) until uptake of gas ceased (4.5 hr). Filtration and evaporation gave a residue which was recrystallized from ethanol to give the ketone (45 g), mp 94–96°.

(ii)—Similar hydrogenation of (±)-13β-ethyl-3-methoxygona-1,3,5(10),8-tetraen-17-one (0.5 g) in methanol (20 ml) and tetrahydrofuran (5 ml) over 10% palladized charcoal (0.2 g) gave the ketone (0.25 g), mp 94–96° (from ethanol), undepressed by the sample prepared as in (i).

(±)-3-Methoxy-8α-estra-1,3,5(10)-trien-17β-ol (5, R = R^1 = CH_3). (i)—(±)-8α-Estrone methyl ether (2 g) was stirred with $NaBH_4$ (1.2 g) in ethanol (200 ml) for 20 min at room temperature and for a further 20 min at reflux. The cooled mixture was acidified with 1 *N* acetic acid and most of the solvent evaporated. Water was added to the residue and the product was filtered off, washed, and dried. Recrystallization from benzene–petroleum ether (bp 60–80°) gave the alcohol (1.5 g), mp 102–103°.

(ii)—(±)-3-Methoxyestra-1,3,5(10),8,14-pentaen-17-one (6 g) was reduced with $NaBH_4$ in ethanol (500 ml) to give (±)-3-methoxyestra-1,3,5(10),8,14-pentaen-17β-ol (**2**, R = R^1 = CH_3) (3.7 g): mp 103–106° (from ether); bp 240° (bath) (3×10^{-4} mm); ν_{max} 3567, 3341, 1603, 1588, and 1558 cm^{-1}. An aliquot (2.3 g) was shaken with hydrogen in ethanol (100 ml) containing 10% palladized charcoal (1.2 g) to give the alcohol (0.8 g), mp 103–104° (from benzene–petroleum ether), undepressed by the sample prepared as in (i).

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TABLE I
(±)-8α-ESTRANE AND (±)-13β-ALKYL-8α-GONANE DERIVATIVES

Type	R	R¹	Mp, °C	Crystn solvent[a]	Method	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H	ν_{max}, mμ (10^{-3} ε)	ν_{max}, cm^{-1}
2	CH_3	CH_3	103–106	A		$C_{19}H_{32}O_2$	80.8	7.9	80.9	8.0	312 (30.7)	
2	n-C_4H_9	CH_3	Gum[b]			$C_{22}H_{38}O_2$	81.4	8.7	81.2	8.7	312 (26.8)	
4	C_2H_5	CH_3	94–96	B	i, ii	$C_{20}H_{36}O_2$	80.5	8.8	80.5	8.6	278 (2.2)	
4	n-C_3H_7	CH_3	133–134	B	i	$C_{21}H_{38}O_2$	80.7	9.0	80.4	8.8	280 (2.3) 287 (2.3)	
4	i-C_3H_7	CH_3	130–131.5	C	i	$C_{21}H_{38}O_2$	81.8	7.8	81.9	7.6		
4	i-C_4H_9	CH_3	142	B + D	i	$C_{22}H_{40}O_2$	80.9	9.2	80.9	9.2	280 (2.2) 288 (2.15)	
4	n-$C_{16}H_{33}$	CH_3	Oil[c]		i	$C_{34}H_{54}O_2$	82.4	10.7	82.5	11.0	280 (1.6)	
4	C_2H_5	H	193–196[d]	B	i	$C_{19}H_{34}O_2$	80.3	8.5	80.2	8.4	279 (2.3) 285 (2.1)	
5	CH_3	CH_3	103–104	F + G	i, ii, iii	$C_{19}H_{30}O_2$	79.7	9.2	79.8	9.2	278 (1.9)	
5	C_2H_5	CH_3	130–133	A + F	i, ii, iii	$C_{20}H_{32}O_2$	79.9	9.4	79.9	9.2	280 (2.2)	
5	C_2H_5	H	192.5–193.5 217–219[e]	C	i	$C_{19}H_{32}O_2$	79.7	9.2	79.6	9.1	287 (2.0)	
5	n-C_3H_7	CH_3	120–121	A + F	i	$C_{21}H_{36}O_2$	80.2	9.6	80.3	9.6		
5	i-C_3H_7	CH_3	64–69	D + H	i	$C_{21}H_{36}O_2$	80.2	9.6	80.7	9.0		
5	n-C_4H_9	CH_3	92–94	A	ii, iii	$C_{22}H_{38}O_2$	80.4	9.8	80.4	9.9		
5	i-C_4H_9	CH_3	137	A + F	i	$C_{22}H_{38}O_2$	80.4	9.8	80.4	9.7	280 (2.0) 287 (1.9)	
5	i-C_5H_{11}	CH_3	66–67	C	i[f]	$C_{23}H_{40}O_2$· $0.5CH_3OH$	78.7	10.1	78.8	10.2	279 (2.2)	
6	C_2H_5	CH_3	131–133	B + C	i	$C_{22}H_{38}O_2$	77.2	8.8	77.3	8.8	279 (1.95)	
9	CH_3	H	143–147	A		$C_{18}H_{28}O_2$	79.1	9.8	79.0	9.4		3472, 1695 1669
9	C_2H_5	H	112.5–113 134–137[f]	E + F		$C_{20}H_{30}O_2$	79.4	10.0	79.4	9.8		3487, 1724, 1667
10	CH_3	H	170–172	G		$C_{18}H_{26}O_2$	78.8	9.6	78.7	9.5		3350, 1700
10	C_2H_5	H	Gum[g]			$C_{19}H_{28}O_2$	79.1	9.8	79.1	9.8		3390, 1709
10	CH_3	C≡CH	185–191	G	i, ii	$C_{20}H_{26}O_2$	80.5	8.8	80.0	8.6		3367, 3215, 2088, 1701
10	C_2H_5	C≡CH	145–152	E + F	i	$C_{21}H_{28}O_2$	80.7	9.0	80.2	9.0		3322, 3185, 1706

[a] A, ether; B, ethanol; C, methanol; D, water; E, benzene; F, petroleum ether (bp 60–80°); G, ethyl acetate; H, acetonitrile. [b] Bp 200–220° (bath) (19×10^{-3} mm). [c] Bp 245–255° (bath) (12×10^{-4} mm). [d] Sometimes a second crystalline form, mp 209–210°, was obtained. [e] Double melting point. [f] Prepared from 13-isopentyl-3-methoxygona-1,3,5(10),8,14-pentaen-17-one by catalytic hydrogenation followed by $NaBH_4$ reduction without purification of the 8α-gona-1,3,5(10)-trien-17-one. [g] Bp 200° (bath) (1×10^{-1} mm).

(iii)—(±)-3-Methoxyestra-1,3,5(10),8-tetraen-17β-ol (0.25 g) was hydrogenated over 10% Pd–C (0.25 g) in methanol (20 ml) and tetrahydrofuran (5 ml) to give the same alcohol (0.25 g), mp 102–104° (from methanol), undepressed by the sample prepared as in (i).

(±)-13β-Ethyl-3-hydroxy-8α-gona-1,3,5(10)-trien-17-one (4, R = C_2H_5; R^1 = H). (i)—Hydrogenation of (±)-13-ethyl-3-hydroxygona-1,3,5(10),8,14-pentaen-17-one as for the corresponding methyl ether gave the ketone, mp 193–196° (from ethanol). A second crystalline form sometimes obtained had mp 209–210°.

(ii)—(±)-13β-Ethyl-3-methoxy-8α-gona-1,3,5(10)-trien-17-one (10 g) was stirred with pyridine hydrochloride (80 g) at 190° for 40 min in an atmosphere of nitrogen. The cooled mixture was shaken with 5% HCl and extracted with chloroform. The organic extract was filtered and evaporated, and the residue was recrystallized from benzene–methanol to give the trienone (6.2 g), mp 201–204°, undepressed by the material prepared as in (i).

(±)-3-Methoxy-8α-estra-2,5(10)-dien-17β-ol (9, R = CH_3; R^1 = H).—(±)-3-Methoxy-8α-estra-1,3,5(10)-trien-17β-ol (28 g) was reduced with lithium (18 g) and ethanol in liquid ammonia–tetrahydrofuran (1000:300 ml). The product was recrystallized from ether to give the dienol (18 g), mp 143–147°. The mother liquors afforded further alcohol (3.0 g), mp 140–143°.

(±)-17β-Hydroxy-8α-estr-5(10)-en-3-one (10, R = CH_3; R^1 = H).—(±)-3-Methoxy-8α-estra-2,5(10)-dien-17β-ol (1 g) was stirred for 1 hr in methanol-water (60:14 ml) containing oxalic acid (from the dihydrate, 1.2 g). Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with ether. The product was recrystallized from ethyl acetate to give the ketone (0.72 g), mp 170–172°.

(±)-17α-Ethynyl-17β-hydroxy-8α-estr-5(10)-en-3-one (10, R = CH_3; R^1 = C≡CH). (i).—(±)-3-Methoxy-8α-estra-2,5(10)-dien-17β-ol (20 g) was refluxed for 3 hr under nitrogen in toluene–cyclohexanone (1300:283 ml) containing aluminum isopropoxide (16.7 g). The product was recrystallized from aqueous methanol to give (±)-3-methoxy-8α-estra-2,5(10)-dien-17-one: mp 106–111° (after softening at 94–96°); ν_{max} 1724, 1695, and 1667 cm^{-1}. The foregoing ketone (10 g) was stirred for 2 hr at room temperature with lithium acetylide–ethylenediamine complex (13.9 g) in dimethylacetamide (1 l., previously saturated with acetylene) through which acetylene was slowly bubbled. The mixture was added to crushed ice–NH_4Cl and extracted with ether. The product was recrystallized from methanol to give (±)-17α-ethynyl-3-methoxy-8α-estra-2,5(10)-dien-17β-ol (8 g): mp 174–182°; ν_{max} 3401, 3205, 1695, and 1667 cm^{-1}. This alcohol (8 g) was stirred for 2 hr in methanol–water (600:90 ml) containing oxalic acid (from the dihydrate, 10.3 g). The product was recrystallized from ethyl acetate to give the required ketone (5.0 g): mp 185–191°; ν_{max} 3367, 3215, 2088, and 1701 cm^{-1}; homogeneous by thin layer chromatography on silica gel in ethyl acetate–hexane (1:1).

The foregoing ketone (0.3 g) was stirred under nitrogen for 3 hr in methanol–concentrated HCl–water (36:2.4:1.6 ml). The total crude crystalline product had infrared absorption bands of comparable intensities at 1704 and 1653 cm^{-1}, and on recrystallization from ethyl acetate the mixture of ketones **10** and **11** (R = CH_3; R^1 = C≡CN) formed crystals (0.15 g): mp 180–192°; λ_{max} 243 mμ (ε 2700); ν_{max} 3367, 3215, 2083, 1701, and 1650 cm^{-1}, the penultimate band being approximately twice as intense as the last band.

Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.5; H, 8.8. Found: C, 80.4; H, 8.8.

(ii)—(±)-3-Methoxy-8α-estra-2,5(10)-dien-17β-ol (3.6 g) was refluxed for 20 hr in benzene (100 ml) containing ethylene glycol (7.2 ml) and 1 toluenesulfonic acid (0.36 g) (Dean–Stark trap). The resulting ketal (3.5 g), mp 118–123°, was kept under nitrogen in pyridine (50 ml) with CrO_3 (3.14 g) for 20 hr. Ethyl acetate was added, and the mixture was filtered through neutral alumina (40 g). Evaporation of the eluate gave a ketone, mp 122–152°. This ketone (3.1 g) was kept overnight in a suspension, previously saturated with acetylene, of $LiAlH_4$ (16 g) in tetrahydrofuran (300 ml).[8b] The mixture was poured on to ice, acidified with 2 *N* H_2SO_4, and extracted with ether. The product was chromatographed on neutral alumina to give an alcohol (2.2 g), mp 160–164° (from ether–petroleum ether). This alcohol (1 g) was refluxed for 10 min in *t*-amyl alcohol–toluene–5 *N* HCl (10:10:40 ml). The organic solvents were evaporated, H_2O was added, and the mixture extracted with ether–ethyl acetate.

The product was chromatographed on neutral alumina to give the ketone (0.39 g): mp 185–190°, undepressed by the sample prepared as in (i); ν_{max} 3378, 3215, 2083, 1704, and 1642 (weak) cm^{-1}.

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Synthesis and Pharmacological Activity of Alkylated Tryptamines[1]

ASHER KALIR[2] AND STEPHEN SZARA

Clinical Neuropharmacology Research Center, National Institute of Mental Health, William A. White Building, St. Elizabeths Hospital, Washington, D. C. 20032

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A series of 3-(N-alkylaminoalkyl-α-methyl)indoles has been prepared either by reductive amination of 3-indolylacetone and 3-indolylbutanone, or by reduction of 3-alkylaminoacylindoles. Introduction of a single methyl group into the aliphatic nitrogen of α-methyltryptamine gave a compound that caused the arousal of motor activity in reserpinized mice in much shorter time than the parent substance. Introduction of a higher group or a second methyl substituent brings about decrease in physiological activity, while elongation of the aliphatic side chain results in complete loss of action.

DL-α-Methyltryptamine (I) has been found to produce LSD-like symptoms in human volunteers.[3] It has been shown that I can be metabolized by converting I to its 6-hydroxy derivative or deaminated to 3-indolylacetone.[4]

The onset of action exerted by I is relatively slow, and the symptoms last longer than those produced by N,N-dialkyltryptamines. The investigations by Vane *et al.*,[5] indicate that the reversal of reserpine-induced ptosis in mice may be a feature common to all tryptamines while the stimulation of spontaneous locomotion in reserpinized mice is restricted to the α-alkylated congeners only.

In a more detailed study of the reversal of reserpine-induced ptosis and the stimulation of spontaneous activity, we have observed that after administration of I the first measure develops rather quickly when compared to the second one which builds up gradually (see Figure 1). The delay between the two effects suggests that the stimulation of motor activity might be due to a metabolite formed slowly from the administered drug. This presumably active metabolite cannot be 6-hydroxy-α-methyltryptamine or indolylacetone since both compounds proved to be inactive in the spontaneous locomotion tests (Table I).

A possible formation of an active metabolite could involve the N-methylation of the side chain of I giving rise to N,α-dimethyltryptamine (N,α-DMT) and N,N,α-trimethyltryptamine (N,N,α-TMT), compounds that might either be active themselves or provide a link toward an active metabolite. This hypothesis has been further substantiated by the fact that the optically active *d* isomer of I exerts a significantly stronger effect than the *l* form, thus pointing to a selective enzymatic pathway of metabolism.[6,7]

We decided to prepare and test a series of N,α-alkyltryptamines and related compounds to determine the effect of changes in the side chain on the physiological activity of these compounds. The synthetic approach followed three routes.

(1) Reaction of indolylmagnesium bromide (III) with propylene oxide, bromination of the resulting 3-indolyl-2-propanol (IV), and condensation of V with an alkylamine. The yield of IV was erratic and only a small amount of N,Nα-trimethyltryptamine (VI, R = R′ = CH_3) was obtained by this method.

(2) Reduction of 3-(2-dimethylaminopropionyl)indole (X) with lithium aluminum hydride. X was prepared from 1,3-di(2-chloropropionyl)indole (IX) and dimethylamine. Bromination of 3-propionylindole (VII)[8] afforded the bromo derivative (VIII) in low yield, contrary to the results with 3-acetylindole.[9]

(3) Reductive amination of 3-indolylacetone (XI)[10] with primary alkylamines. This method gave N,α-DMT (VI, R = H; R′ = CH_3) and the corresponding N-ethyl and N-isopropyl derivatives in acceptable yields. Analogously 1-(3-indolyl)-3-butanone afforded the homologous 3-(3-alkylaminobutyl)indoles.

In connection with this and other investigations a number of tryptamines were required. The preparation of previously unreported N-hexyl- and 6-hydroxy-N,N-diethyl derivatives is described in the Experimental Section of this paper.

(1) Portions of this study were presented at the 46th Annual Meeting of the Federation of American Societies for Experimental Biology, Atlantic City, N. J., April 1962, and at the 33rd Meeting of the Israel Chemical Society, Be'er Sheva, Dec 1963.

(2) Visiting Scientist, Clinical Neuropharmacology Research Center, National Institute of Mental Health, May 1961–1963. Israel Institute for Biological Research, Ness Zionah, Israel.

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(4) S. Szara, *Federation Proc.*, **20**, 885 (1961); *Experientia*, **17**, 76 (1961).

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(6) We are indebted to Dr. H. Schwarz of Sandoz Pharmaceuticals for these isomers.

(7) After completion of the present study a similar observation has been reported for α-ethyltryptamine: G. Vogel and L. Ther, *Arzneimittel-Forsch.*, **13**, 779 (1963).

(8) W. C. Anthony, *J. Org. Chem.*, **25**, 2049 (1960).

(9) K. Bodendorf and A. Walk, *Arch. Pharm.*, **294**, 484 (1961).

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