a 50% reduction in spontaneous activity were: IVc, 82; IVd, 69; IVf, 100; IVh, 133.

The 3-alkoxypyridazine derivatives all produced depression, except VIh which produced an initial stimulation followed by depression. The doses (mg./kg.) producing a 50% reduction in spontaneous activity were: VIc, 145; VIf, 59; VIh, 80.

Subsequent pharmacological studies being made include the rotarod technique to determine the degree of impairment of forced motor and coordinated activity, and the determination of the effects of experimental compounds on hexobarbital sleeping time and on pentylenetetrazol and strychnine convulsions in mice.

Experimental

3-Alkoxy-6-chloropyridazines (III).—Sodium (4.6 g., 0.2 g.-atom) was dispersed in 70 ml. of hot anhydrous xylene and the appropriate anhydrous alcohol (0.22 mole) was added over a period of 20 min. After all the sodium had reacted, a solution of 29.8 g. (0.20 mole) of 3,6-dichloropyridazine (II) prepared and purified by the method of Coad and Coad[6] in 50 ml. of anhydrous xylene was added over a period of 15 min. The internal temperature was kept below 60° by cooling during the addition. The mixture was heated at 60° for 10 hr., cooled to room temperature, and filtered. The xylene was removed *in vacuo*, and the residue was distilled through an efficient column.

The conditions were modified slightly for the preparation of IIIg. The internal temperature was raised to 95° during the last 6 hr. of heating. In the case of IIIh the xylene filtrates were washed with two 25-ml. portions of cold 30% NaOH solution and dried (Na_2SO_4) before distillation through the column. Certain of these compounds were reported previously[7] (see Table I).

3,6-Bisalkoxypyridazines (IV).—These could have been prepared directly from dichloropyridazine (II) with excess sodium alkoxide by traditional procedures described in the literature.[4b] In the particular cases in this series, the compounds were prepared by addition of a second mole of alkoxide for each mole of 3-alkoxy-6-chloropyridazine used. The temperature was raised to the boiling point of xylene for 3 hr. The mixture was cooled and filtered. The filtrate was concentrated *in vacuo*, dissolved in ethanol, hydrogenated in a Parr apparatus with ammonium hydroxide and activated 10% palladium on carbon, filtered, and concentrated *in vacuo*. The residue was distilled through an efficient column separating traces of pyridazine and monoalkoxypyridazine from the product. The yields ranged from 75–87%.

3-Alkoxy-6-(2-dimethylaminoethoxy)pyridazines (V).—Sodium (2.3 g., 0.10 g.-atom) was dispersed in 100 ml. of hot anhydrous xylene. To this was added 0.11 mole of the appropriate anhydrous alcohol. The mixture was stirred until the sodium disappeared and was heated to boiling. A solution consisting of 20 g. (0.10 mole) of IIIh and 50 ml. of anhydrous xylene was added over a period of 5 min. for lower alkoxides and 15 min. for higher ones. The reaction mixture was stirred and heated under reflux for 3 hr., cooled, and filtered. The filtrate was washed with 10 ml. of cold 30% NaOH solution and dried (Na_2SO_4). The xylene and excess alcohol were removed *in vacuo*. The purification of this crude product had to be varied for the different alkoxides. Compounds Va, Vd, Vf, and Vg were simply distilled through an efficient column. In the case of Vg, it was necessary to equip the side-arm condenser with a steam jacket since the product melts at 39–41°.

In the cases of Vb and Vc, the crude product was first freed from the halopyridazines which would interfere with the final distillation by hydrogenolysis in a Parr apparatus with 5 ml. of concentrated ammonium hydroxide, 2.0 g. of activated 10% palladium on carbon, and 100 ml. of ethanol. The ethanol was removed *in vacuo*, and the residue was washed with cold 10% NaOH solution and extracted with four 100-ml. portions of ether. The combined extracts were dried (Na_2SO_4), filtered through fresh sodium sulfate, and flash distilled to remove the solvent. The residue was then distilled through an efficient column.

(6) P. Coad and R. Coad, *J. Org. Chem.*, **28**, 1919 (1963).
(7) T. Itai and H. Igeta, *Yakugaku Zasshi*, **74**, 1195 (1954).

Hydrogenolysis of Halopyridazines.—The Parr hydrogenation apparatus was used in the hydrogenolysis of 3,6-dichloropyridazine to form pyridazine (I) which was purified by the method of Coad, *et al.*[3] It was also used for the preparation of 3-alkoxypyridazine (VIc, VIf, and VIh) by the hydrogenolysis of the appropriate 3-alkoxy-6-chloropyridazine (0.1 mole) using 50 ml. of ethanol, 10 ml. of concentrated ammonium hydroxide, and 5 g. of activated palladium on carbon at 3 atm. pressure. The mixture was filtered after cooling and the filtrate was slowly distilled. Absolute ethanol was added from time to time until a total of 800 ml. had been distilled and 80 ml. remained. The liquid was cooled, filtered, and distilled through an efficient column. The yields ranged from 78–84%.

Acknowledgment.—The authors wish to thank C. Jelleff Carr for his interest in this project and are indebted to Miss June Hyepock for assistance in the synthesis and to Dr. Jack Campion of Riker Laboratories for analytical data. Pharmacological studies at the University of Pittsburgh were supported by Public Health Research Grant MH-03029 from the National Institute of Mental Health.

Novel Oral Hypoglycemic Agents. I. Hexahydroindeno[1,2-*c*]pyrroles and Indanamines[1]

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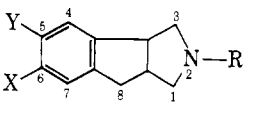
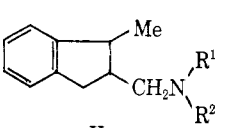
In a previous paper[3] the synthesis of some 1,2,3,3a,-8,8a-hexahydro-2-alkylindeno[1,2-*c*]pyrroles (I), a new class of heterocyclic compounds, was described, and their potential amoebicidal activity was investigated. Maximum *in vitro* amoebicidal activity of these compounds was $^1/_{32}$ that of emetine hydrochloride. To our surprise 1,2,3,3a,8,8a-hexahydro-2-butyl-5,6-dimethoxyindeno[1,2-*c*]pyrrole hydrochloride was found to possess high oral hypoglycemic activity in experimental animals. This observation led the authors to investigate systematically the oral hypoglycemic activity among other compounds of this class. It has been found that N-butyl compounds are the most active ones, though other alkyl substitutions also exhibit oral hypoglycemic activity. The results of the investigation are listed in Table I. From the table it appears that compounds **5**, **6**, **8**, and **11** are active.



I



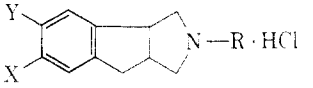
II

In order to ascertain whether the hexahydroindeno-[1,2-*c*]pyrrole structure is essential for the development of oral hypoglycemic activity, a few compounds of the type II have also been prepared. It has been found that two compounds of this class also possess appreci-

(1) This investigation was partly supported by the award of a scholarship to one of the authors (S. C. L.) by the Ministry of Education, Government of India.
(2) To whom inquiries regarding this paper should be sent.
(3) K. L. Pathak and B. Pathak, *J. Indian Chem. Soc.*, **38**, 253 (1961).

TABLE I

ORAL HYPOGLYCEMIC ACTIVITY OF 1,2,3,3a,8,8a-HEXAHYDROINDENO[1,2-*c*]PYRROLES



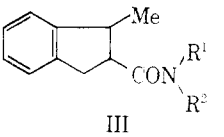
I

No.	X	Y	R	No. of animals used	Av. % fall of blood sugar[a] 25 mg./kg.
1	H	H	Ethyl[b]	4[c]	12 ± 2.5
2	H	H	*n*-Propyl[b]	4[c]	10 ± 3.1
3	H	H	*n*-Butyl[b]	11[c], 4[d]	10 ± 1.7, 27.8 ± 3.7
4	H	H	*n*-Hexyl	4[c]	8.7 ± 1.3
5	H	H	Cyclohexyl	4	18.6 ± 2.5
6	H	H	Benzyl	5[c]	16 ± 5.5
7	OMe	H	Ethyl	4	12 ± 5.0
8	OMe	H	*n*-Propyl	7	18 ± 2.8
9	OMe	H	*n*-Butyl	11, 3[d]	13.4 ± 2.1, 8
10	OMe	H	*n*-Hexyl	4	12.5 ± 3.4
11	OMe	OMe	*n*-Butyl[b]	8,[c] 11[d]	14.35 ± 1.4, 36.3 ± 5.9
12	Tolbutamide			8[c]	22.5 ± 2.6

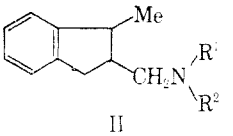
[a] Blood sugar was estimated by Hagedorn and Jensen's method [*Biochem. Z.*, **135**, 46 (1923); **137**, 92 (1923)]. [b] See ref. 3. [c] Normal rabbits. [d] Alloxan diabetic rabbits.

TABLE II

1-METHYLINDAN-2-CARBOXAMIDES AND 1-METHYLINDAN-2-ALKYLAMINES



III



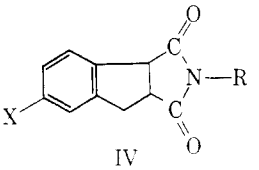
II

Compd.	R^1	R^2	B.p., °C. (mm.)	Formula	% carbon Calcd.	% carbon Found	% hydrogen Calcd.	% hydrogen Found	% nitrogen Calcd.	% nitrogen Found	Average % fall of blood sugar[a]
III	Ethyl	Ethyl	140–141 (0.4)	$C_{15}H_{21}NO$	77.9	77.6	9.0	8.9	6.06	5.81	
III	*n*-Propyl	*n*-Propyl	160–162 (0.8)	$C_{17}H_{25}NO$	78.7	78.5	9.6	9.3	5.41	5.08	
III	*n*-Butyl	*n*-Butyl	176–180 (1.0)	$C_{19}H_{29}NO$	79.4	79.1	10.1	10.2	4.88	4.61	
III	*n*-Propyl	H	172–175 (0.6)	$C_{14}H_{19}NO$	77.4	77.2	8.8	9.0	6.54	6.55	
III	*n*-Butyl	H	184–186 (0.2)	$C_{15}H_{21}NO$	77.9	77.6	9.1	9.2	6.06	6.17	
II	Ethyl	Ethyl	97–98 (0.3)	$C_{15}H_{23}N$	82.9	83.1	10.6	10.8	6.45	6.28	25.7 ± 4.3
II	*n*-Propyl	*n*-Propyl	115–116 (0.6)	$C_{17}H_{27}N$	83.2	82.9	11.0	10.9	5.71	5.95	23.2 ± 4.9
II	*n*-Butyl	*n*-Butyl	130–134 (0.6)	$C_{19}H_{31}N$	83.5	83.3	11.4	11.2	5.13	4.88	14.8 ± 1.3
II	*n*-Propyl	H	123–126 (1.5)	$C_{14}H_{21}N$	82.8	82.5	10.3	10.5	6.89	7.01	
II	*n*-Butyl	H	132–135 (0.7)	$C_{15}H_{23}N$	82.9	83.1	10.6	10.9	6.45	6.25	
II	*n*-Propyl	Methyl	118–120 (0.8)	$C_{15}H_{23}N$	82.9	82.7	10.6	10.8	6.45	6.66	13.6 ± 2.8
II	*n*-Butyl	Methyl	180–182 (0.6)	$C_{16}H_{25}N$	83.1	82.8	10.8	11.0	6.06	5.89	12.5 ± 2.5

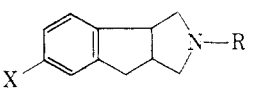
[a] Eight normal rabbits were used in each case. The hydrochloride was given orally at 20 mg./kg.

TABLE III

INDAN-1,2-DICARBOXY-N-ALKYLIMIDES AND 1,2,3,3a,8,8a-HEXAHYDROINDENO[1,2-*c*]PYRROLES



IV



V

Compd.	X	R	B.p., °C (mm.)	M.p., °C.	Formula	% carbon Calcd.	% carbon Found	% hydrogen Calcd.	% hydrogen Found	% nitrogen Calcd.	% nitrogen Found
IV	H	*n*-Hexyl	177–179 (1.2)		$C_{17}H_{21}NO_2$	75.3	75.1	7.7	7.9	5.1	5.4
IV	H	Cyclohexyl	188–190 (0.8)		$C_{17}H_{19}NO_2$	75.5	75.3	7.0	7.2	5.2	5.3
IV	H	Benzyl	194–196 (0.6)		$C_{18}H_{15}NO_2$	78.0	78.2	5.4	5.7	5.0	5.2
IV	OMe	Ethyl	178–180 (1.0)		$C_{14}H_{15}NO_3$	68.5	68.3	6.1	6.4	5.7	6.0
IV	OMe	*n*-Propyl	181–183 (0.6)		$C_{15}H_{17}NO_3$	69.5	69.2	6.5	6.8	5.4	5.2
IV	OMe	*n*-Butyl	180–182 (0.7)		$C_{16}H_{19}NO_3$	70.3	70.6	6.9	6.6	5.1	4.9
IV	OMe	*n*-Hexyl	162–164 (0.9)		$C_{18}H_{23}NO_3$	71.7	72.0	7.6	7.4	4.6	4.8
V	H	*n*-Hexyl	138–142 (0.6)	149–151	$C_{17}H_{25}N \cdot HCl$	72.9	72.6	9.3	9.4	5.0	4.8
V	H	Cyclohexyl	144–145 (0.6)	206–208	$C_{17}H_{23}N \cdot HCl$	73.5	73.4	8.6	8.3	5.0	4.8
V	H	Benzyl	154–156 (0.6)	187–189	$C_{18}H_{19}N \cdot HCl$	75.6	75.7	7.0	7.1	4.9	4.9
V	OMe	Ethyl	128–130 (0.6)	188–190	$C_{14}H_{19}NO \cdot HCl$	66.2	66.0	7.8	7.9	5.5	5.8
V	OMe	*n*-Propyl	165–167 (0.7)	146–148	$C_{15}H_{21}NO \cdot HCl$	67.2	67.1	8.2	8.4	5.2	5.6
V	OMe	*n*-Butyl	165–166 (0.6)	154–156	$C_{16}H_{23}NO \cdot HCl$	67.8	67.6	8.5	8.6	4.9	5.2
V	OMe	*n*-Hexyl	163–165 (0.9)	132–134	$C_{18}H_{27}NO \cdot HCl$	69.7	69.9	9.0	9.3	4.5	4.7

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[3] (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°.[6] 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.

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

17α-Methylandrostane-3α,17β-diol

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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]

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

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