(Fig. 4) with a slope of −5002 kcal./mole, confirming the usefulness of the method.

Four points should be emphasized concerning kinetic studies on drug substances in suspension.

1. Data should be reported as "amount degraded" rather than "amount remaining" or "percentage lost," since (for example) for a given drug substance a suspension having a potency of 20 mg./ml. will degrade at the same rate as one containing 10 mg./ml. but the "percentage lost" is one-half as much.

2. If the drug substance under study is acidic or basic, it will often act as the primary buffer in the system, since solid drug substance is always in excess.

3. Because the solvent system is saturated with drug substance, concentrations of degradation products may reach a point where they affect the reaction rate, causing deviations from zero-order kinetics as the reaction proceeds.

4. In those cases where the simplified method fails because the system is dissolution rate limited, it may help to: (*a*) use a batch of drug substance with smaller particle size, and (*b*) agitate the stored samples. Estimations of room temperature stability based upon such conditions will err on the safe side.

CONCLUSION

Using the simplified procedure (for systems obeying the underlying assumptions stated under *Theory*), the room temperature stability of a drug substance in suspension can be estimated from elevated temperature studies (measuring amount degraded at various times) without determining solubilities or first-order rate constants. When the assumptions are not valid for a particular system, the abbreviated method will not work. The procedure is being presented here so that its applicability can be tested by investigators concerned with evaluating the stability of drug substances in suspension or suspension formulations.

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Hydrindene Derivatives as Potential Oral Hypoglycemic Agents: *N*-Alkyl 1,2,3,3a,4,8b-Hexahydroindeno[1,2-*b*]pyrroles

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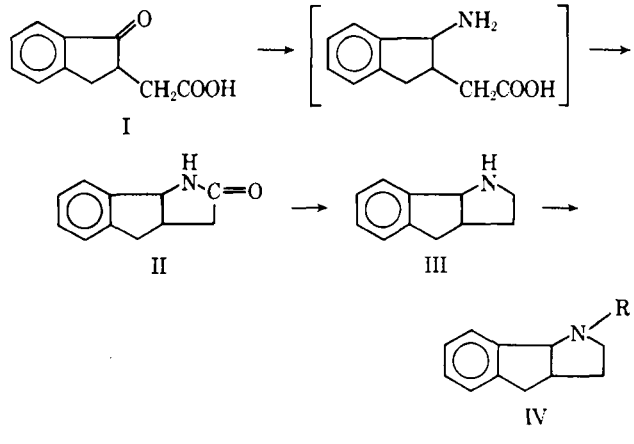
Abstract □ A number of hexahydroindeno[1,2-*b*]pyrroles were synthesized and biologically evaluated. Only two compounds of this series showed some weak oral hypoglycemic activity. However, one compound inhibited epinephrine biosynthesis *in vitro* appreciably.

Keyphrases □ Hydrindene derivatives—*N*-alkyl 1,2,3,3a,4,8b-hexahydroindeno[1,2-*b*]pyrroles synthesized and screened as potential oral hypoglycemic agents □ *N*-Alkyl 1,2,3,3a,4,8b-hexahydroindeno[1,2-*b*]pyrroles—synthesized and screened as potential oral hypoglycemic agents □ Hypoglycemic agents, oral, potential—synthesis and screening of *N*-alkyl 1,2,3,3a,4,8b-hexahydroindeno-[1,2-*b*]pyrroles □ Heterocyclic compounds—synthesis of new class of hydrindene derivatives

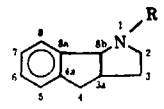
In continuation of an investigation on hydrindene derivatives as potential oral hypoglycemic agents (1), it was considered worthwhile to synthesize isomeric indeno[1,2-*b*]pyrroles and test their activity. This new type of heterocyclic compound, although prepared earlier by different routes without any alkyl substitution at the nitrogen atom (2–4), was synthesized, in high yield (Scheme I), by a novel route by way of reductive amination.

1-Keto-2-indanylacetic acid (I) (5, 6), on being subjected to reductive amination with hydrogen and dry ammonia gas in absolute ethanol in the presence of Raney nickel catalyst, yields the corresponding pyrrolidone (II) in one step. Pyrrolidone (II), after reduction with lithium aluminum hydride in dry tetrahydrofuran, gives indeno[1,2-*b*]pyrrole (III). The pyrrolidone (II) shows the characteristic C=O and N—H stretching vibrations, while the indenopyrrole (III) shows only the N—H stretching vibrations. The indenopyrroles were



Scheme I

Table I—*N*-Alkyl 1,2,3,3a,4,8b-Hexahydroindeno[1,2-*b*]pyrroles (IV)



Compound Number	R	Boiling Point	Formula	Analysis, % Calc.	Found	Melting Point of Picrate
1	CH_3[a]	140°/1.2 mm.	$C_{12}H_{15}N$	C 83.26 H 8.67 N 8.09	82.94 8.92 7.94	158–160°
2	C_2H_5[a]	83–85°/0.45 mm.	$C_{13}H_{17}N$	C 83.43 H 9.09 N 7.49	83.21 9.38 7.13	141–143°
3	*n*-C_3H_7[a]	92°/0.5 mm.	$C_{14}H_{19}N$	C 83.58 H 9.45 N 6.97	83.71 9.51 6.62	115–117° dec.
4	*n*-C_4H_9[b]	82–85°/0.3 mm.	$C_{15}H_{21}N$	C 83.73 H 9.77 N 6.51	84.02 9.92 6.18	103–105°

[a] Iodide was used. [b] Bromide was used.

treated with the appropriate alkyl halide and purified by tosylation to furnish the respective *N*-alkyl indenopyrroles (IV).

ACTIVITY

Four compounds were synthesized in this series; only *n*-propylhexahydroindeno[1,2-*b*]pyrrole (IV: R = *n*-propyl) caused a 12% blood sugar lowering at a dose level of 250 mg./kg. body weight in normal, overnight fasted rabbits while the butyl derivative (IV: R = *n*-butyl) caused a 10% lowering. The blood sugar was estimated at 0, 2, and 4 hr. Tolbutamide was a standard in this test, and it caused a reduction of about 40% of the blood sugar at a dose of 250 mg./kg.

In another test, inhibition of epinephrine biosynthesis *in vitro* from norepinephrine, the hydrochloride of 1,2,3,3a,4,8b-hexahydroindeno[1,2-*b*]pyrrole (III), caused a 73.1% inhibition of phenylethanolamine-*N*-methyltransferase activity (7) at a concentration of 1×10^{-4} *M*.

EXPERIMENTAL[1,2]

2-Oxo-1,2,3,3a,4,8b-hexahydroindeno[1,2-*b*]pyrrole (II)—1-Keto-2-indanylacetic acid (I, 0.3 mole) was subjected to reductive amination in the presence of absolute ethanol (300 ml.) containing dry ammonia gas (16%) and Raney nickel (10 g.) at a hydrogen pressure of 150 atm. at 125°. After the reaction, which required nearly 8 hr., the mass was separated from the catalyst by filtration, ethanol was removed by distillation, and the residual mass was repeatedly washed with water and finally crystallized from hot water as shining white crystals, m.p. 191–193°; ν_{max} 1652 (C=O) and 2975 (NH) $cm.^{-1}$.

Anal.—Calc. for $C_{11}H_{11}NO$: C, 76.32; H, 6.36; N, 8.09. Found: C, 76.02; H, 6.58; N, 7.88.

1,2,3,3a,4,8b-Hexahydroindeno[1,2-*b*]pyrrole (III)—Pyrrolidone (II, 1 mole) was reduced with lithium aluminum hydride (0.6 mole) in dry tetrahydrofuran for 10–12 hr. and worked up in the usual way. The indenopyrrole distilled at 99–101°/0.6 mm. as a colorless liquid; ν_{max} 2950 $cm.^{-1}$ (NH). Picrate darkens at 182° and melts at 224–226° dec.

Anal.—Calc. for $C_{11}H_{13}N$: C, 83.04; H, 8.18; N, 8.80. Found: C, 82.87; H, 8.42; N, 9.03.

***N*-Alkyl 1,2,3,3a,4,8b-Hexahydroindeno[1,2-*b*]pyrrole (IV)**—Indenopyrrole (III, 1 mole) was heated in a sealed tube with the appropriate alkyl halide (1.1 moles) on a water bath for 8–12 hr. and then poured into water and extracted with benzene. It was then tosylated with *p*-toluenesulfonyl chloride (1 mole) in benzene solution under stirring at 40° with simultaneous addition of sodium hydroxide (10%) to keep the mass alkaline. The benzene layer was separated out, and the tertiary amine was repeatedly extracted with hydrochloric acid (6 *N*). The combined acid extracts were basified with sodium hydroxide under cooling, extracted with ether, and dried over anhydrous sodium sulfate, and the amine was distilled under reduced pressure to furnish colorless liquids (Table I).

[1] All melting points are uncorrected.
[2] IR spectra were recorded in mineral oil mulls using a Perkin-Elmer spectrophotometer.

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