Search for Potential Oral Hypoglycemic Agents: Synthesis and Activity of 2-(*N*-Alkylaminomethyl)indolizines

A. U. DE▲ and B. P. SAHA

Abstract □ Some 2-(*N*-alkylaminomethyl)indolizines were synthesized and biologically evaluated; however, they showed very weak oral hypoglycemic activity. One compound of this series possessed anti-Parkinson activity and another had marginal anti-inflammatory activity.

Keyphrases □ 2-(*N*-Alkylaminomethyl)indolizines—synthesized and screened as potential oral hypoglycemic agents □ Indolizines, 2-(*N*-alkylaminomethyl)—synthesized and screened as potential oral hypoglycemic agents □ Hypoglycemic agents, oral, potential—synthesis and screening of 2-(*N*-alkylaminomethyl)indolizines

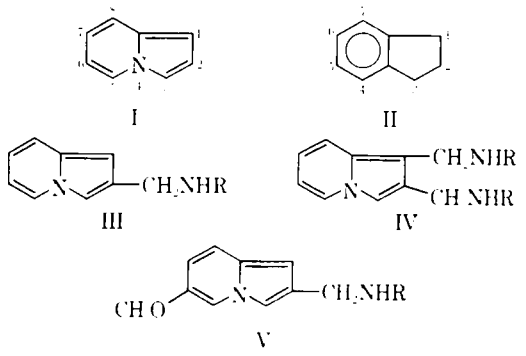
The alkaloids vincamine, vindoline, and vindolinine obtained from plants of the genus vinca, commonly known as periwinkles, have been reported to cause varying degrees of blood sugar lowering (1–4). All of these alkaloids are structurally different from the common hypoglycemic agents like sulfonylureas and biguanides and thus provide a new lead in this area (4).

DISCUSSION

The structures of these alkaloids consist of several ring systems like those of indolizine, quinolizine, indole, and quinoline. Since indolizine ring systems (I) are a rare occurrence in natural products, their presence in vinca alkaloids is of particular interest. It appears from the literature that no indolizine derivative has yet been tested as a potential oral hypoglycemic agent.

Indolizine derivatives have been reported to exhibit hypotensive, anti-inflammatory, central nervous system depressant, anticholinergic, antiedema, estrogenic, and anabolic activities (5–11). In addition, both the pyridine and the pyrrole ring systems, the structural components of the indolizine ring linked through the common nitrogen atom, have furnished various pharmacologically active compounds through their derivatives. Moreover, the indolizine ring system may be regarded as structurally equivalent to the hydrindene ring system (II) through isosteric replacement of one angular carbon atom of the hydrindene ring with a nitrogen atom. From the point of chemical reactivity, indolizine and hydrindene rings have one common feature: the 1- and 3-positions of both ring systems are active in their many derivatives (12–14). Presumably, these may combine with the active receptor site through these positions and evoke biological responses.

The significance of the hydrindene ring system for oral hypoglycemic activity (15) and various other activities (16, 17) has been already established. Earlier, the authors synthesized and biologically evaluated a few hydrindene derivatives as potential oral hypoglycemic agents; however, the results were not encouraging (18, 19). The interesting features of the indolizine ring system have shifted emphasis to indolizine derivatives as potential oral hypoglycemic agents. With this objective, the synthesis and biological evaluation of a few compounds (III, IV, and V) have been undertaken. These derivatives were chosen to keep the 1- and/or 3-positions free so as to retain their reactivity in the biological system.



In this article, only the synthesis and biological activity of 2-(*N*-alkylaminomethyl)indolizines (III) are described. The synthesis and activity of other indolizine derivatives (IV and V) will be described in a subsequent report.

Indolizine-2-carboxylic acid (III*a*) was prepared by the condensation of α-picoline with ethyl bromopyruvate according to the method of Borrows and Holland (20), who obtained a buff-colored product. But in this case, a greenish product of the same melting point as reported earlier (20) was obtained. All attempts to convert this acid to the corresponding acid chloride failed. As such, the acid was converted to the corresponding methyl indolizine-2-carboxylate (III*b*) by the reaction of diazomethane with a suspension of the acid (III*a*) in ether instead of dioxane (20). The ester was condensed with the respective amines to give 2-(*N*-alkylcarboxamido)indolizines (III*c*) and then reduced with lithium aluminum hydride to 2-(*N*-alkylaminomethyl)indolizines (III) in dry ether (Scheme I). On standing, the colors of the carboxamides (III*c*) and the amine (III) changed to dark brown. UV absorption characteristics are recorded in Table I.

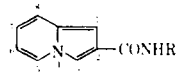
Table I—UV Absorption Characteristics

Compound	λ_{max}, nm. (in Alcohol)	ϵ_{molar}
III*a*	290, 300, 342	1972, 2173, 2124
III*b*	291, 301, 342	2358, 2668, 2581
III*c* (R = ethyl)	288, 300, 341	1406, 1438, 1363
III (R = ethyl)	284, 296, 346	2610, 2870, 1866

ACTIVITY

Of the four compounds synthesized, 2-(*N*-*n*-butylaminomethyl)-indolizine (III: R = *n*-butyl) and 2-(*N*-*n*-propylaminomethyl)-indolizine (III: R = *n*-propyl) exhibited one-fourth of the activity of tolbutamide at 250 mg./kg. body weight in normal, overnight-fasted rabbits. The blood sugar was estimated at 0, 2, and 4 hr. Because of this weak hypoglycemic acitivity, further investigations were suspended. However, 2-(*N*-ethylaminomethyl)indolizine (III: R = ethyl) demonstrated anti-Parkinson activity as determined by the oxotremorine model in mice. The activity was seen at doses that were very close to lethality. The minimum effective dose (MED) was 50 mg./kg. i.p., and the lethal dose (LD_{50}) in mice was 140 mg./kg.

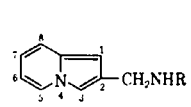
Table II—2-(*N*-Alkylcarboxamido)-indolizines (III*c*)



Compound	R	Melting Point	Boiling Point
1	Methyl[a]	178–180°	—
2	Ethyl[b]	112–114°	—
3	*n*-Propyl[b]	78–80°	195–197°/0.5 mm.
4	*n*-Butyl[b]	70–72°	179–181°/0.5 mm.

[a] Crystallized from dilute ethanol. [b] Crystallized from benzene–petroleum ether (b.p. 60–80°).

Table III—2-(*N*-Alkylaminomethyl)indolizines (III)



Compound	R	Boiling Point	Formula	Analysis, % Calc.	Found
1	Methyl	108–110°/0.6 mm.	$C_{10}H_{12}N_2$	C 75.00	74.65
				H 7.50	7.73
				N 17.50	17.26
2	Ethyl	100–102°/0.7 mm.	$C_{11}H_{14}N_2$	C 75.88	76.03
				H 8.05	8.37
				N 16.10	15.81
3	*n*-Propyl	123–125°/0.55 mm.	$C_{12}H_{16}N_2$	C 76.60	76.45
				H 8.51	8.82
				N 14.89	15.21
4	*n*-Butyl	140–142°/0.8 mm.	$C_{13}H_{18}N_2$	C 77.21	76.88
				H 8.91	9.09
				N 13.87	13.58

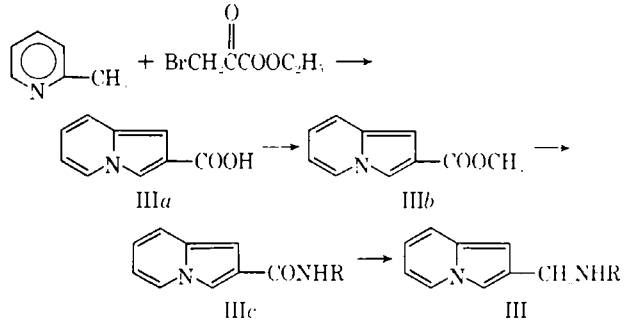
i.p. Thus, further studies were suspended. On the other hand, 2-(*N*-*n*-propylaminomethyl)indolizine (III: R = *n*-propyl) demonstrated marginal anti-inflammatory activity but only at rather large oral doses in rats. Due to this weak activity, further studies were not undertaken. All of these compounds showed no microbiological activity.

EXPERIMENTAL[1]

Methyl Indolizine-2-carboxylate (III*b*)—To a suspension of indolizine-2-carboxylic acid (III*a*, 10 g.) in dry ether (250 ml.), an ethereal solution of diazomethane was added in the usual way. The reaction was allowed to continue overnight, and the resulting solution was filtered. The solvent was removed when a yellowish product was obtained, which crystallized from dilute ethanol as colorless plates, m.p. 98–99°.

2-(*N*-Alkylcarboxamido)indolizines (III*c*)—Methyl indolizine-2-carboxylate (III*b*, 1 mole) and the appropriate alkylamine (1.5 moles) were heated in a hard glass, sealed tube on a water bath for 12–16 hr. After cooling, the reaction mass was poured into water, either filtered or extracted with benzene, and washed with water. The crude product was either crystallized from dilute ethanol or benzene–petroleum ether (b.p. 60–80°) or distilled under reduced pressure to yield white to pale-yellow solids (Table II).

2-(*N*-Alkylaminomethyl)indolizines (III)—2-(*N*-Alkylcarboxamido)indolizine (III*c*, 1 mole) was reduced with lithium aluminum hydride (0.6 mole) in sodium-dried ether for 16 hr. and worked up in the usual way. The crude amines were purified by distillation to yield colorless products (Table III).



Scheme I

[1] All melting points are uncorrected. Absorption characteristics were recorded on a Spectromom 201 spectrophotometer made in Hungary.

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▲ To whom inquiries should be directed.