The average daily dose of dichlorodiphenyltrichloroethane, 3.7 mg. (3.5 mg. given in the feeding study + 0.2 mg., the average daily intake in food), was substituted for I in Eq. 4. The assumption was thus tacitly made that all of the administered pesticide was actually absorbed. The mean content of pesticide found in body fat, 613 mg., was taken to represent the body total, since other work showed that over 95% of body dichlorodiphenyltrichloroethane is dissolved in the fat (8).

To estimate the degree of accumulation of pesticides in the general population, it was assumed that administration occurs with meals, three times a day. R was calculated by Eq. 11, using a value of 1/3 day for τ and the values for $t_{1/2}$ given in Table I. The values of R, also shown in Table I, indicate that the degree of accumulation of the organochlorine pesticides is indeed high. In the case of dieldrin, for example, repeated dosing causes the average body level to rise to 1600 times the value that would result after a single dose.

The pesticides treated in this study have been widely used in agriculture. Although toxic effects have not been demonstrated in volunteers receiving doses many times higher than those to which the general population is at present exposed, the safety of these chemicals in humans is still open to question. Organochlorine pesticides have been shown to elicit pharmacological effects in animals and are blamed for decreases in the population of several species, including the bald eagle. In a sense, widespread use of persistent pesticides represents an uncontrolled experiment on man and other animals. The extremely long half-lives of these materials and their consequent accumulation in man, coupled with their slow degradation in the environment, make us extremely vulnerable if it should turn out that they are not as safe in man as their proponents would have us believe.

REFERENCES

(1) J. Robinson, *Ann. Rev. Pharmacol.*, **10**, 353(1970).

(2) E. Nelson, *J. Pharm. Sci.*, **50**, 181(1961).

(3) C. G. Hunter, J. Robinson, and M. Roberts, *Arch. Environ. Health*, **18**, 12(1969).

(4) J. G. Wagner, *J. Clin. Pharmacol.*, **7**, 84(1967).

(5) J. G. Wagner, J. I. Northam, C. D. Alway, and O. S. Carpenter, *Nature*, **207**, 1301(1965).

(6) J. M. Van Rossum, *J. Pharm. Sci.*, **57**, 2162(1968).

(7) W. J. Hayes, W. F. Durham, and C. Cueto, *J. Amer. Med. Ass.*, **162**, 890(1956).

(8) M. L. Schafer and J. E. Campbell, in "Organic Pesticides in the Environment," American Chemical Society, Washington, D.C., 1966, p. 89.

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p-Substituted 1,2-Diphenylindolizines as Anti-Inflammatory Agents

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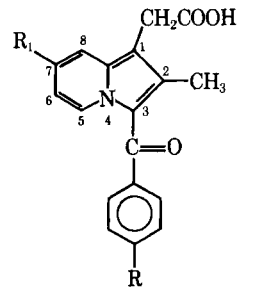
Abstract □ In an effort to explore indolizines as potential medicinal agents, some *p*-substituted 1,2-diphenylindolizines were prepared. These compounds were designed to be investigated for possible anti-inflammatory activity. The syntheses were accomplished *via* the Chichibabin–Stepanow synthesis, using the properly substituted benzylpyridines and phenacyl bromides.

Keyphrases □ 1,2-Diphenylindolizines, *p*-substituted—synthesized and screened as potential anti-inflammatory agents □ Anti-inflammatory agents, potential—synthesis of *p*-substituted 1,2-diphenylindolizines, pharmacological screening □ Indolizines, *p*-substituted 1,2-diphenyl—synthesized and screened as potential anti-inflammatory agents

Considerable interest in the fundamental chemistry of the indolizine heterocyclic system has been generated by the publications of Boekelheide and coworkers (1–4). In contrast to the study of this aspect of the indolizine system, there have been only scattered reports of the biological activity of indolizines and no systematic study has been reported (5–7). Buu-Hoï and Xuong (8) considered 2-(4-fluoro-2-methylphenyl)indolizine and 2-(4-fluoro-2-methylphenyl)-7-methylindolizine as carcinogens, but they failed to mention whether these compounds were actually tested for carcinogenic properties. Buu-Hoï *et al.* (9) reported that 2-(4-cyclohexylphenyl)-indolizine was noncarcinogenic when painted on the skin of experimental animals.

Carbon and Brehm (10) considered 1-indolizinealanine as a tryptophan antimetabolite. Cardellini *et al.* (11) reported that, in preliminary tests, indolizine-1-



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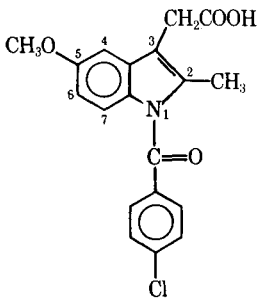

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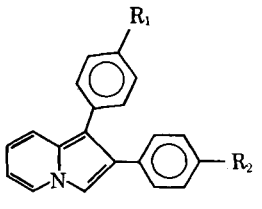

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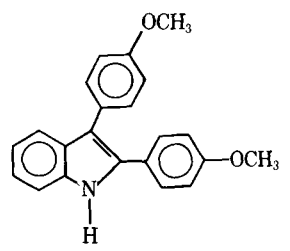

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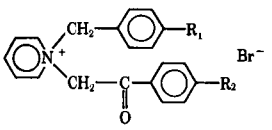


Table I—Pyridinium Bromides

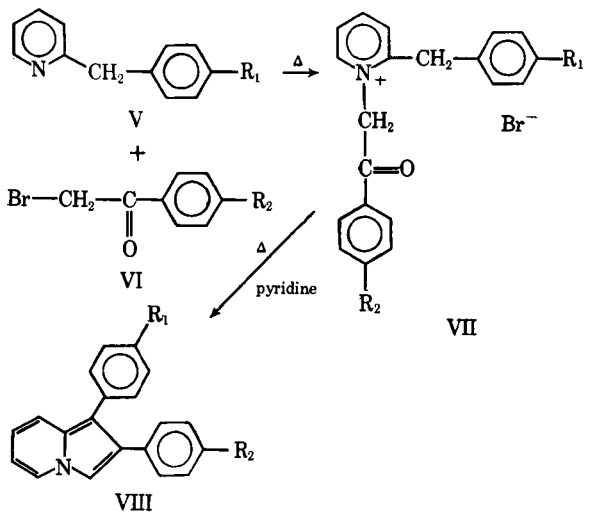
Compound Number	R_1	R_2	Melting Point	Yield, %	Formula	Analysis, % Calc.	Found
1	—H	$-CH_3$	184–186°	39	$C_{21}H_{20}BrNO$	C 65.98 H 5.27 N 3.66	66.08 5.36 3.62
2	$-OCH_3$	$-CH_3$	199–201°	33	$C_{22}H_{18}BrNO_2$	—[a]	
3	$-OCH_3$	—Br	196–197°	59	$C_{21}H_{19}Br_2NO_2$	—[a]	
4	$-OCH_3$	—Cl	210–212°	28	$C_{21}H_{19}BrClNO_2$	—[a]	
5	—Cl	$-CH_3$	220–221°	28	$C_{21}H_{19}BrClNO$	—[a]	
6	—Cl	—Cl	210–211°	46	$C_{20}H_{16}BrCl_2NO$	—[a]	
7	$-CH(CH_3)_2$	$-OCH_3$	107–110°	62	$C_{24}H_{26}BrNO_2$	—[a]	
8	$-OCH_3$	—H	186–187°	80	$C_{21}H_{20}BrNO_2$	—[a]	

[a] IR spectra were consistent with the assigned structures. The compounds were further characterized by conversion to the corresponding indolizine for which IR and NMR spectra were obtained that were consistent with the assigned structures. In addition, satisfactory elemental analyses for the indolizines were obtained. See Table II.

acetic acid, the structural analog of indole-3-acetic acid (heteroauxin), showed some auxinlike activity. Saldabols *et al.* (12) reported in 1970 that 5-bromo- and 5-nitrofuryl derivatives of indolizine possessed activity against both Gram-positive and Gram-negative bacteria.

Walter and Margolis (13) found no useful activity for some 1-aminoalkyl-2-phenylindolizines, which were screened for their effects on the CNS in mice and, in some instances, in cats; the compounds were stimulants at low doses, were depressants at higher doses, and caused death by convulsions. 2,3-Bis(*p*-methoxyphenyl)-indolizines were reported to possess antiexudative activity (14). In 1968, Buu-Hoï and Hien (15) reported that, when tested in rats, 2-(4-fluoro-3-methylphenyl)-indolizine decreased the duration of paralysis caused by the drug zoxazolamine.

Certain indolizine-1-acetic acids (I) have been reported to exhibit analgesic and anti-inflammatory activities (16). The structural similarity of these indolizines to indomethacin (II) suggests that the shift of the "indole nitrogen" (in indomethacin) to the bridgehead position may not destroy the elementary constitution of the molecule needed for anti-inflammatory action. This encouraged us to prepare several indolizine analogs (III) of 2,3-bis(*p*-methoxyphenyl)indole (IV) (indoxole), reported to be of interest as an anti-inflammatory agent (17).



Scheme I

DISCUSSION

All the compounds prepared were *p*-substituted 1,2-diphenylindolizines (Table II, Compounds 9–16). They were prepared from the properly substituted 2-benzylpyridines (V) and phenacyl bromides (VI) *via* the Chichibabin–Stepanow synthesis (18) (Scheme I). The 2-benzylpyridine and phenacyl bromide were combined, resulting in the formation of a pyridinium bromide salt (VII) (Table I, Compounds 1–8) which was cyclized in hot pyridine to the corresponding indolizine. The indolizines were unstable in light, especially when in a chloroform solution.

Venturella (19, 20) prepared other *p*-substituted 1,2-diphenylindolizines by similar procedures. A mechanism for the Chichibabin–Stepanow synthesis was postulated by Bragg and Wibberly (21).

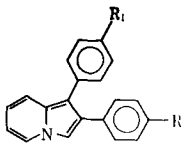
EXPERIMENTAL[1]

The necessary 2-benzylpyridines were prepared by the procedures described by Sperber *et al.* (22). The phenacyl bromides were prepared by bromination of the corresponding acetophenone in methanol (23).

Synthesis of Pyridinium Bromides (Table I)—The pyridinium bromides (VII) were prepared by mixing the phenacyl bromides (VI) with an approximately 5% molar excess of the 2-benzylpyridines (V). The mixture was liquified on a steam bath, allowed to cool to room temperature, and then refrigerated (−5°) for 3–5 days under an atmosphere of dry nitrogen. The resulting tan to brown cake was dissolved in a minimum of hot 95% methanol, and the solution was refrigerated (−5°) for about 3 days. Occasionally it was necessary to promote precipitation of the quaternary salt by concentration of the methanolic solution under reduced pressure and/or addition of anhydrous ether. Most often, the salt that formed was an off-white powdery substance. If an amorphous substance formed, it usually could be precipitated in the desired form by triturating with anhydrous ether and refrigerating (−5°) the resulting mass for several days. Recrystallization of the salts was accomplished from boiling acetone. Where a satisfactory analytical sample could not be obtained, the compounds were characterized by conversion to the corresponding indolizines. IR spectra for the qua-

[1] All melting points were determined on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Elemental analyses were performed by F. B. Strauss Microanalytical Laboratory, Oxford, England. IR spectra were recorded on a Beckman IR-8 spectrometer, and NMR spectra were recorded on a Varian HA-100 NMR spectrometer. Spectra were recorded for the indolizines and the pyridinium bromides and are consistent with assigned structures.

Table II—Indolizines



Compound Number[a]	R_1	R_2	Melting Point	Yield, %	Formula	Analysis, % Calc.	Found
9	—H	—CH_3	120–121°	90	$C_{21}H_{17}N$	C 89.01	89.09
						H 6.05	6.02
						N 4.94	4.82
10	—OCH_3	—CH_3	103–104°	63	$C_{22}H_{19}NO$	C 84.32	84.26
						H 6.11	6.14
						N 4.47	4.49
11	—OCH_3	—Br	138–139°	62	$C_{21}H_{16}BrNO$	C 66.68	66.54
						H 4.26	4.18
						N 3.70	3.71
12	—OCH_3	—Cl	125–126°	79	$C_{21}H_{15}ClNO$	C 75.56	75.68
						H 4.83	4.90
						N 4.20	4.25
13	—Cl	—CH_3	130–133°	69	$C_{21}H_{16}ClN$	C 79.36	79.56
						H 5.07	4.98
						N 4.41	4.40
14	—Cl	—Cl	168–169°	93	$C_{20}H_{13}Cl_2N$	C 71.02	70.87
						H 3.87	3.91
						N 4.14	4.15
15	—$CH(CH_3)_2$	—OCH_3	151–152°	73	$C_{24}H_{26}NO$	C 84.42	84.22
						H 6.79	6.78
						N 4.10	4.10
16	—OCH_3	—H	94–95°	62	$C_{21}H_{17}NO$	C 84.25	84.19
						H 5.72	5.68
						N 4.68	4.71

[a] IR and NMR spectra were consistent with the assigned structures.

ternary salts were consistent with the assigned structures. Satisfactory elemental analyses and IR and NMR spectra for the corresponding indolizines were consistent with the assigned structures.

Synthesis of Indolizines (Table II)—The pyridinium bromides (VII) were converted to the corresponding indolizines (III) by heating the salt with an excess of pyridine on a steam bath until a clear yellow solution formed (usually 15–20 min.). The pyridine solvent was then removed under reduced pressure, and the yellow to orange residue was recrystallized from methanol or ethanol. Final recrystallization was accomplished with petroleum ether (b.p. 35–70°).

PHARMACOLOGIC EVALUATION

2-(*p*-Methylphenyl)-1-phenylindolizine (Compound 9) and 2-(*p*-bromophenyl)-1-(*p*-methoxyphenyl)indolizine (Compound 11) were tested for anti-inflammatory activity in a mycobacterium-induced, adjuvant arthritis screen[2]. Both were found to be inactive relative to the reference compound, indoxole.

REFERENCES

(1) A. Galbraith, T. Small, and V. Boekelheide, *J. Org. Chem.*, **24,** 582(1959).

(2) V. Boekelheide and A. Miller, *ibid.*, **26,** 431(1961).

(3) V. Boekelheide and R. J. Windgassen, *J. Amer. Chem. Soc.*, **81,** 1456(1959).

(4) R. J. Windgassen, W. H. Saunders, and V. Boekelheide, *ibid.*, **81,** 1459(1959).

(5) W. B. Harrell and R. F. Doerge, *J. Pharm. Sci.*, **56,** 225 (1967).

(6) *Ibid.*, **57,** 1989(1968).

(7) W. B. Harrell, *J. Pharm. Sci.*, **59,** 275(1970).

(8) N. P. Buu-Hoï and N. D. Xuong, *J. Chem. Soc.*, **1953,** 386.

(9) N. P. Buu-Hoï, L. C. Bink, T. B. Loc, N. D. Xuong, and P. Jacquignon, *ibid.*, **1957,** 3126.

(10) J. A. Carbon and S. Brehm, *J. Org. Chem.*, **26,** 3376(1961).

(11) M. Cardellini, S. Ottolino, and P. Tafaro, *Ann. Chim. (Rome)*, **58,** 1206(1968); through *Chem. Abstr.*, **70,** 77753a(1969).

(12) N. Saldabols, L. N. Alekseeva, B. Brizga, L. Kruzmetra, and S. Hillers, *Khim. Farm. Zh.*, **4,** 20(1970); through *Chem. Abstr.*, **73,** 77136p(1970).

(13) L. A. Walter and P. Margolis, *J. Med. Chem.*, **10,** 498(1967).

(14) W. Engel, E. Seeger, H. Teufel, and A. Eckenfels, German pat. 1,922,191 (Nov. 12, 1970); through *Chem. Abstr.*, **74,** 12995w(1971).

(15) N. P. Buu-Hoï and D. P. Hien, *Biochem. Pharmacol.*, **17,** 1227(1968).

(16) J. H. C. Nayler, British pat. 1,174,124 (Dec. 10, 1969); through *Chem. Abstr.*, **72,** 55285p(1970).

(17) J. Szmuszkovicz, E. M. Glenn, R. V. Heinzelman, J. B. Hester, Jr., and G. A. Youngdale, *J. Med. Chem.*, **9,** 527(1966).

(18) A. E. Chichibabin and E. N. Stepanow, *Chem. Ber.*, **62,** 1068 (1929).

(19) V. S. Venturella, *J. Pharm. Sci.*, **52,** 868(1963).

(20) *Ibid.*, **53,** 1166(1964).

(21) D. R. Bragg and D. G. Wibberly, *J. Chem. Soc.*, **1962,** 2627.

(22) N. Sperber, D. Papa, E. Schwenk, and M. Sherlock, *J. Amer. Chem. Soc.*, **73,** 3856(1951).

(23) M. C. Rebstock and E. L. Pfeiffer, *ibid.*, **74,** 3209(1952).

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