Arylindolizines III

Methoxyl and Glyoxyl Derivatives of Several Substituted Phenylindolizines

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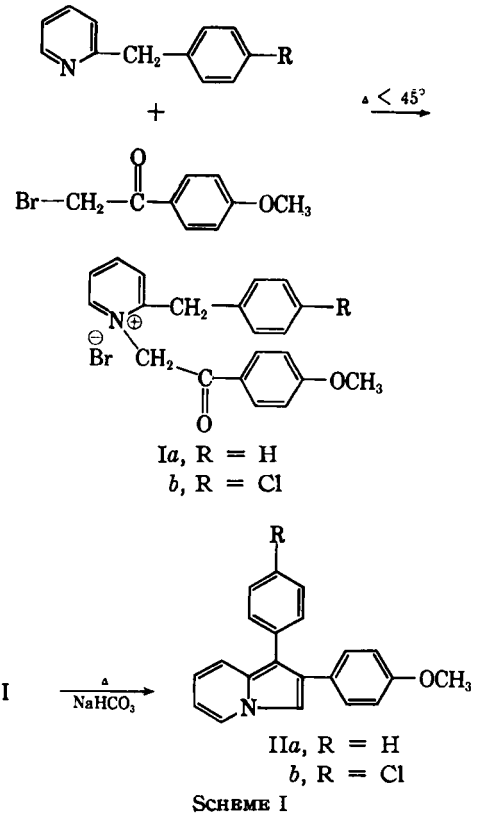
4-Methoxyphenacylbromide reacts in good yield with 2-benzylpyridine and 2-(4'-chlorobenzyl) pyridine in the Tschitschibabin synthesis to form the corresponding indolizines. The methyl ethers are cleaved with difficulty to the corresponding phenolic compounds which have anomalous solubility characteristics. Arylindolizines with an open 1 position react in good yield with ethoxalylchloride to form the corresponding ethyl glyoxylates.

As a continuation of the search for arylindolizines of possible psychotherapeutic activity (1, 2), it was desired to prepare compounds containing a nuclear methoxyl group and compounds containing the —COCOX moiety in the 1 position, where X = —OEt, —OH, or —N⟨ ⟩. Since previous efforts (1) to prepare II*a* by nuclear substitution of the corresponding bromo compound failed, it was decided to test the Tschitschibabin method (3) for the preparation of compounds II*a* and II*b* from the appropriate phenacyl compound[1] according to the reactions in Scheme I.

Compounds II*a* and II*b* formed in good yield in this procedure under mild conditions. In each case, 4-methoxphenacylbromide condensed with the 2-substituted pyridine with constant shaking at 35–45°. The condensation was accompanied by a small amount of decomposition inherent in the use of both starting materials. Cyclodehydration proceeded readily from this stage in refluxing $NaHCO_3$ solution. During the formation of I*b*, if the temperature was permitted to rise above 40°, spontaneous cyclodehydration occurred, preventing isolation of the intermediate. This phenomenon was experienced in previous work (1) employing 2-(4'-chlorobenzyl) pyridine; but the reaction was not temperature dependent, mostly because condensation could not be affected at below cyclodehydration temperatures.

Hydrolysis of II*a* and of II*b* to the corresponding phenols proceeded under vigorous treatment with 30% HBr/HOAc. Separation of the sodium salts of the phenols depended upon their insolubility in the aqueous basic media in the presence of ether. A portion of the phenol remained in the acidic form and was recovered from the ether extract. Both II*a* and II*b* gave distinct green when tested with anhydrous $FeCl_3$ in $CHCl_3$ (4).

Attempts to apply the reactions in Scheme I to 2-methoxyphenacylbromide resulted in failure to effect condensation when using either 2-benzylpyridine or 2-(4'-chlorobenzyl)pyridine. In each instance black intractable tars resulted at condensation temperatures ranging from 40 to 110°. Similar failures resulted during attempts at condensation at −5° for 2 weeks and 4 weeks and also at room temperature for 4 weeks. Failure of the condensation to occur presumably is due



SCHEME I

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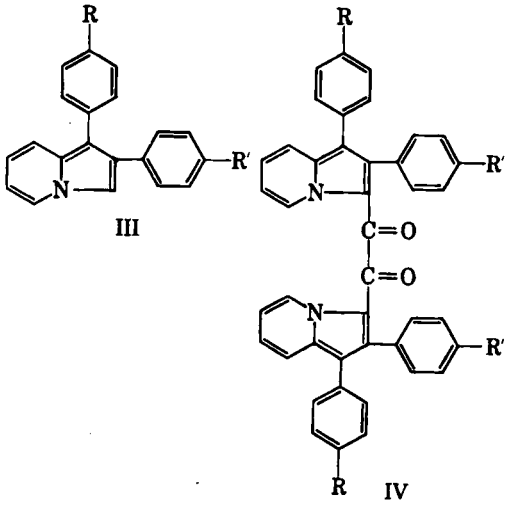
to steric effects, since the electronic effect of an —OCH_3 in the 2 position is not markedly different from the 4 position.

The purity of the starting pyridines greatly affected the yield and purity of condensation product and ease of isolation of the subsequent indolizine during this study. Failure to purify the pyridine compounds resulted in as much as a 15–20% reduction in yield of the intermediate pyridinium bromide. In addition, the decreased yield was accompanied subsequently by the formation of a green indolizine, which showed a low elemental analysis and a qualitatively identical infrared spectrum.

The synthesis of glyoxylic derivatives of previously prepared arylindolizines (1) of general structure III was carried out to test the efficacy of preparing carbonyl derivatives which would



III *a*, R = H, R′ = Br
b, R = Cl, R′ = Br
c, R = H, R′ = NO_2
d, R = Cl, R′ = NO_2

lead easily to several derived functions. This approach was used to establish whether the arylindolizines would react easily with $ClCOCO_2Et$ (5) or if the longer less specific method of Galbraith (6) would be necessary. In the latter method, indolizine was reported to react with ClCOCOCl in a 2:1 ratio to form a diketone similar to IV (2 and 3 positions unsubstituted) in 15% yield. Evaporation of the reaction liquor followed by sublimation of the remaining solid gave an unreported yield of indolizylglyoxalylchloride. For the present study, the desired ethyl esters would have to be prepared from the corresponding indolizylglyoxalylchloride by ethanolysis. Thus, in addition to the formation of a small amount of by-product of type IV, the yield of the esters would presumably have been decreased by the longer procedure. Once the keto esters were prepared, it then seemed likely that the corresponding acids and amide derivatives could be formed easily.

The reaction with $ClCOCO_2Et$ took place in the manner anticipated. Unexpectedly, III*d* reacted to form the glyoxyl derivative in fair yield. The formation of this compound was not anticipated because previous attempts to form the corresponding benzoyl compound resulted in failure (1). The success of the reaction of $ClCOCO_2Et$ in this case must come from the increased strength of the ethylglyoxylium ion $(EtO_2C-\overset{\oplus}{C}=O)$ as an electrophile since the failure of C_6H_5COCl (1) and its *meta* amd *para* NO_2 derivatives (2) to form an acyl derivative was presumably due to the electronic effects of the *p*-Cl and *p*-NO_2 group on the formation of the necessary nucleophile of the indolizine.

The hydrolysis of the ethylglyoxylates of III was effected in aqueous NaOH suspension of the compounds; the resulting sodium salts of the acids were insoluble in the excess NaOH present. The products of these reactions remained as insoluble solids along with unreacted starting material and could be separated from the parent ethyl esters by the solubility of the acid salt in hot water.

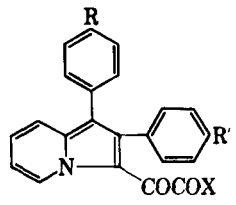
Recrystallization of the glyoxylic acids was accompanied by a large amount of decomposition if the primary solvent was too hot or if the acid was allowed to stand in the hot solvent for more than 5–10 minutes before cooling. In each case the product turned dark-green to brown. This was especially true of 1-glyoxyl-2-(4′-nitrophenyl)-3-phenylindolizine and its 3-(4″-chlorophenyl) analog.

In a limited number of experiments it was impossible to form the *N,N*-diethylglyoxamides, even in the absence of solvent. However, similar reactions employing piperidine resulted in fair to good yields of the corresponding piperidino compounds. In this procedure, the unreacted indolizine largely decomposed to gummy materials which were easily separated from the product.

The analytical data for the ethylglyoxylates, the corresponding acids, and piperidinoxalyl derivatives of III are given in Table I.

Several attempts at applying this general method of indolizine synthesis to substituted phenacylchlorides resulted in failure to effect the required condensation necessary to form the pyridinium intermediates. Representatives of this group of compounds include *m*-nitrophenacylchloride and 3,4-dihydroxyphenacylchloride.

TABLE I.—SUBSTITUTED ACYL DERIVATIVES OF ARYLINDOLIZINES OF THE TYPE



R	R'	X	M.p., ° C.	Yield, %	LS[a]	RS[b]	Anal. Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	Br	OEt	190–192	71	...	*A*	64.43	4.03	3.13	64.42	3.97	3.06
Cl	NO_2	OEt	215.5–216.5	52	*A*	*A*	64.29	3.79	6.25	64.22	3.73	6.23
Cl	Br	OEt	179.5–180	62	*B*	*A*	60.00	3.52	2.90	60.28	3.40	2.87
H	NO_2	OEt	193–194	95	*B*	*A*	69.57	4.35	6.76	69.39	4.47	7.20
H	Br	OH	179–180	92	...	*B*	62.86	3.33	3.33	62.56	3.68	3.96
Cl	NO_2	OH	193–195	96	...	*C*	62.85	3.09	6.67	63.26	3.22	6.92
Cl	Br	OH	174.5–75.5	95	...	*D*	58.15	2.86	3.08	58.24	3.02	3.20
H	NO_2	OH	168–169	96	...	*E*	68.39	3.63	7.25	67.94	3.57	7.06
H	Br	$C_5H_{10}N$[c]	189–190	59	*C*	*A*	66.53	4.72	5.75	66.73	4.77	5.73
Cl	NO_2	$C_5H_{10}N$	174–75.5	91	*D*	*C*	66.53	4.52	8.62	66.31	4.74	8.23
Cl	Br	$C_5H_{10}N$	178.5–79.5	96	*E*	*A*	62.19	4.22	5.37	62.39	4.41	5.04
H	NO_2	$C_5H_{10}N$	186–187	91	*D*	*F*	71.25	5.08	9.27	71.45	5.11	8.85

[a] Leaching solvent: *A*, cold absolute EtOH; *B*, EtOH (−5° C.); *C*, Et_2O (0° C.); *D*, high boiling petroleum ether (at 50° C.); *E*, low boiling petroleum ether. [b] Recrystallization solvent: *A*, absolute EtOH; *B*, Et_2O-petroleum ether (30–60°); *C*, hot C_6H_6; *D*, warm C_6H_6-petroleum ether (30–60°) (1:1); *E*, 50% EtOH; *F*, warm C_6H_6, followed by Me_2CO-H_2O. [c] Piperidyl.

These failures are consistent with literature reports (7) which indicate an increased condensing power with decreasing electronegativity of the halide.

The pharmacological activity of the reported compounds is currently being investigated.

EXPERIMENTAL[2]

2-Benzyl-4′-methoxyphenacylpyridinium Bromide (Ia).—Fifty grams (0.22 mole) of 4-methoxyphenacylbromide was mixed with 75 Gm. (2 equivalents) of 2-benzylpyridine and heated at 40–45° with constant stirring for 40 minutes. The dark brown cake resulting was refrigerated for 3 days, broken up, and leached with 250 ml. of hot ethanol. The yellowish slurry was then filtered and washed with 50 ml. of ice-cold acetone to yield 55.5 Gm. (65%) of a yellowish-white solid, m.p. 227–230° dec. The melting point was raised to 241–242° dec., after recrystallization from hot acetone.

Anal.—Calcd. for $C_{21}H_{20}BrNO_2$: C, 63.47; H, 5.04; N, 3.53. Found: C, 63.40; H, 5.14; N, 3.76.

2-(4′-Methoxyphenyl)-3-phenylindolizine (IIa).—Forty grams of *Ia* was placed in a 3-L. three-necked flask equipped with an addition funnel, a stirrer, and a water condenser and mixed with 1.5 L. of saturated sodium bicarbonate solution. The mixture was stirred and heated under reflux for 6 hours. Any foaming that took place was controlled by the addition of ethanol as needed (volume of ethanol should not exceed 30 ml.). The mixture was allowed to stand at room temperature overnight. Filtration and washing of the solid with 500 ml. of hot water gave a greenish-yellow solid which was recrystallized from acetone-H_2O to give 23 Gm. of yellowish-white flakes, m.p. 97–98°. An additional 5 Gm. was obtained by overnight refrigeration of the recrystallization liquor. The total yield was 93%. If a green gum forms on standing, separate from the bulk of the solid, dry in air overnight, pulverize, and recrystallize from acetone-H_2O.

Anal.—Calcd. for $C_{21}H_{17}NO$: C, 84.28; H, 5.69; N, 4.68. Found: C, 84.18; H, 5.77; N, 4.95.

2-(4′-Chlorobenzyl)-4″-methoxyphenacylpyridinium Bromide (Ib).—Fifty grams (0.22 mole) of 4-methoxyphenacylbromide was mixed with 2 equivalents of 2-(4′-chlorobenzyl)pyridine as described above, warmed to 40° and stirred for 8 min. The light tan solid cake was cooled immediately in ice and, when the reaction subsided (as evidenced by the cessation of fuming), placed in the refrigerator and allowed to stand for 2 days. The solid was then fragmented and dissolved in 250 ml. of hot methanol. The solution was evaporated to 1/3 volume, placed at −10° for 3 hours, and filtered with suction to give 20.5 Gm. of product. The filtrate was diluted with an equal volume of ether and filtered to give an additional 41 Gm. The solids were combined washed with 100 ml. of ice-cold ether, dried, washed with 100 ml. of iced water, dried with suction, and then dried overnight over $CaCl_2$. Recrystallization from hot acetone gave 58.5 Gm. of snow white flakes, m.p. 231–232° dec. (64%).

Anal.—Calcd. for $C_{21}H_{19}ClBrNO_2$: C, 58.33; H, 4.63; N, 3.24. Found: C, 58.54; H, 4.51; N, 3.13.

2-(4′-Chlorophenyl)-3-(4″-methoxyphenyl)indolizine (IIb).—Forty-two grams (0.097 mole) of *Ib* was stirred and refluxed in the manner previously described with 2.5 L. of saturated sodium bicarbonate solution for 4 hours and the suspension allowed to stand overnight. Filtration, followed by washing with three 300-ml. portions of hot water and

[2] All melting points were taken on a Fisher-Johns apparatus and are uncorrected. Microanalyses by Swartzkopf Microanalytical Laboratories, Woodside, N. Y.

air drying for 60 hours, gave 30.5 Gm. (93%) of light tan solid. The product recrystallized from 50% ethanol in long gray needles, m.p. 118.5 to 119.5°.

Anal.—Calcd. for $C_{21}H_{16}ClNO$: C, 75.60; H, 4.81; N, 4.19. Found: C, 75.41; H, 4.76; N, 3.85.

2-(4′-Hydroxyphenyl)-3-phenylindolizine.—Twenty-five grams (0.084 mole) of II*a* was mixed with 100 ml. of 30% hydrobromic acid in acetic acid in a two-necked flask equipped with a stirrer and water condenser; the mixture was refluxed for 6 hours with constant stirring. The resultant dark green suspension was suction filtered and the precipitate pulverized and macerated 3 hours with water, then filtered to give a 30% recovery of starting material. The original acidic filtrate was poured slowly into 300 ml. of iced 5 *N* sodium hydroxide solution and mixed with 150 ml. of ether. The mixture was filtered, the precipitate mixed with enough cold water to effect solution, acidified with hydrochloric acid to give a solid which was dissolved in benzene. The benzene was dried over anhydrous sodium sulfate and evaporated to give a dark oil which changed to a brownish-yellow solid (solid *A*) when triturated with 50 ml. of petroleum ether (30–60°). The ether-sodium hydroxide mixture was separated. The ether layer dried and evaporated to give a brown oil, which changed to a brown gum when triturated with petroleum ether. The gum was allowed to dry in air overnight, pulverized, washed with petroleum ether, and air dried to give a brownish-yellow solid (*B*). Solid *A* weighed 6 Gm. and *B* weighed 6.2 Gm. (total 51% yield). Each was crystallized from hot benzene-petroleum ether to give dark yellow flakes, m.p. 157–158° dec. after drying at 85° for 1 hour. (Mixed melting point *A* and *B*, 156–157° dec.)

Anal.—Calcd. for $C_{20}H_{15}NO$: C, 84.30; H, 5.26; N, 4.92. Found: C, 84.44; H, 5.18; N, 4.71.

2-(4′-Hydroxyphenyl)-3-(4″-chlorophenyl)indolizine.—Twenty grams (0.062 mole) of II*b* was treated with 75 ml. of 30% hydrobromic acid in acetic acid as described above. After 6-hours reflux, the dark green solution was allowed to stand overnight. Filtration gave 1.8 Gm. of starting material. The filtrate was poured onto 300 ml. of iced sodium hydroxide solution (5 *N*), extracted with 150 ml. of ether, and processed as above. The ether layer was separated, dried, and evaporated to give a dark green gum. The gum was triturated with petroleum ether (30–60°), filtered, pulverized, and washed with 500 ml. of petroleum ether. Total yield was 13.2 Gm. of a brown powder which was carefully recrystallized from ethanol-water to give tan plates, m.p. 130–131° (mixed melting point with starting material 105–107°).

Anal.—Calcd. for $C_{20}H_{14}ClNO$: C, 75.23; H, 4.39; N, 4.39. Found: C, 75.08; H, 4.20; N, 4.09.

General Method for Preparation of the Ethylglyoxylates of III.—Into a 250-ml. three-necked flask equipped with a stirrer, water condenser, and dropping funnel was added 0.06 mole of the appropriate indolizine suspended in 100 ml. of benzene. The mixture was stirred and heated to reflux, at which time 1.05 *M* equivalents of ethoxalyl chloride was added all at once. The dark solution was refluxed for 90 minutes and allowed to cool and stand overnight. The mixture was processed by a modification of a previously described method (5). The dark solution was poured into 500 ml. of ice water and the mixture suction filtered to remove a portion of the impure product (with III*b*, this solid was unreacted starting material). The layers of the filtrate were separated, and the aqueous layer was washed with 10–30-ml. portions of chloroform. The organic phases were combined, washed with 200 ml. of water, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to give a solid product. The combined solid was then leached, dried in air, recrystallized, and dried under vacuum.

Hydrolysis of the Ethylglyoxylates of III.—One-hundred milliliters of 5 *N* sodium hydroxide was added to 2.5 Gm. of the appropriate ethylglyoxylate derivative contained in a two-necked 250-ml. flask equipped with a stirrer and water condenser, and the mixture was stirred at reflux for 10 hours (eight hours with ethyl 2-(4′-bromophenyl)-3-phenylindolizylglyoxylate). The suspension was cooled and filtered. The precipitate suction dried, then suspended in 500 ml. of water for 1 hour at 60°, then overnight at room temperature. The suspension was filtered, the filtrate treated with 6 *N* hydrochloric acid to pH 5 and allowed to cool in the refrigerator for 3–5 hours. The resulting suspension was suction filtered, the solid washed with 200 ml. of water, and thoroughly dried and recrystallized from the appropriate solvent.

Reaction of the Ethylglyoxylates of III with Piperidine.—Five grams of the ethylglyoxylate was mixed with 100 ml. of piperidine in a 150-ml. distilling flask and refluxed for 12 hours under a water condenser. The mixture was cooled and allowed to stand overnight. Any insoluble tars that formed were filtered out, and the filtrate was evaporated under reduced pressure to remove the excess piperidine. The oil which remained was triturated with low boiling petroleum ether until it was transformed into a thick gum or powdery solid. The partially purified solid was then allowed to dry in air, leached with 150 ml. of solvent, suction filtered until dry, and recrystallized to give the corresponding 2,3-disubstituted piperidinoxalylindolizine.

REFERENCES

(1) Venturella, V. S., This Journal, 52, 868(1963).
(2) *Ibid.*, 53, 107(1964).
(3) Tschitschibabin, A. E., *Ber.*, 60, 1607(1927).
(4) Cheronis, N. D., and Entrikin, J. B., "Semimicro Qualitative Organic Analysis," 2nd ed., Interscience Publishers, Inc., New York, N. Y., 1957, p. 228.
(5) Holland, D. O., and Nayler, J. H. C., *J. Chem. Soc.*, 1955, 1504.
(6) Galbraith, A., *et al.*, *J. Am. Chem. Soc.*, 83, 453(1961).
(7) Mosby, W. L., "Heterocyclic Systems with Bridgehead Nitrogen Atoms, Part 1," Interscience Publishers, Inc., New York, N. Y., 1961, pp. 240–241; Moser, K. B., and Bradsher, C. K., *J. Am. Chem. Soc.*, 81, 2547(1959).