[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NEW MEXICO]

Synthesis of Some 2-(3-Indolylethenyl)- and 2-(2-Pyrrylethenyl)-Pyridines and Hydrogenated Analogs

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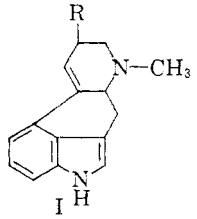
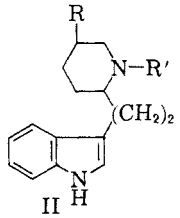
Under Knoevenagel conditions a number of substituted 2-picolinium iodides were condensed with indole-3-aldehyde and with pyrrole-2-aldehyde. Several 2-(3-indolylethenyl)-1-alkyl-5-substituted pyridinium iodides were catalytically reduced to give the corresponding indolylethylpiperidines. These compounds were prepared for their potential physiological activity In addition, a number of new 5-substituted 2-picolinium iodides and substituted 6-methylnicotinamides are described.

The physiological activity of derivatives of lysergic acid (Ia) prompted the synthesis of compounds possessing the general structural formula (II).



I



II

Ia. R = COOH
Ib. R = $CON(C_2H_5)_2$

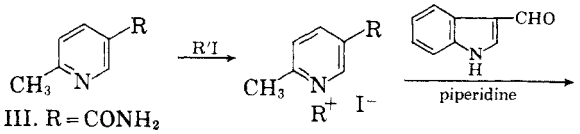
IIa. R = H, R′ = CH_3
IIb. R = H, R′ = C_2H_5
IIc. R = $COOC_2H_5$, R′ = CH_3
IId. R = $CONHC_2H_5$, R′ = CH_3
IIe. R = $CON(C_2H_5)_2$, R′ = CH_3

In 1954, Akkerman and Veldstra[2] prepared VII (R=H, R′=CH_3) by condensing indole-3-aldehyde and 2-picolinium iodide in the presence of piperidine. Subsequent hydrogenation of VII (R=H, R′=CH_3) produced IIa. This reaction was not further explored by these workers. However, Finkelstein and Lee[3] followed the same procedure with the appropriately substituted picolinium iodide to produce IIc. As an alternate approach Gray and Archer[4] allowed indole to react with 2-vinylpyridine in acidic media. They obtained 2-(3-indolylethyl)pyridine which upon quaternization with methyl iodide and subsequent hydrogenation produced (IIa).

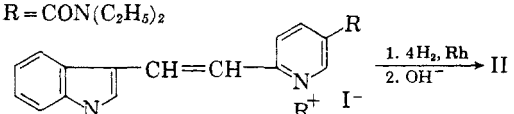
The marked physiological activity of LSD (lysergic acid diethylamide) (Ib) prompted the synthesis of the analog IIe. This was best accomplished by the method of Akkerman and Veldstra.[2] In addition to IIe, compounds IIb and IId were prepared.

A number of new 6-methylnicotinamides were prepared as intermediates. These were obtained by the permanganate oxidation of aldehyde collidine by a modification of the method of Graf[5] followed by esterification and subsequent treatment of the ester with the appropriate amine. However, in the preparation of VI, ethyl 6-methylnicotinate was saponified with potassium hydroxide. Potassium 6-methylnicotinate was allowed to react with oxalyl chloride whereupon the 6-methylnicotinoyl chloride was obtained. This was not isolated but allowed to react with diethylamine.

These amides, as well as the 5-alkyl-2-picolines were quaternized with methyl iodide or with ethyl iodide. The quaternary salts were smoothly condensed in refluxing methanol with indole-3-aldehyde or with pyrrole-2-aldehyde using piperidine as a catalyst.



III. R = $CONH_2$
IV. R = $CONHCH_3$
V. R = $CONHC_2H_5$
VI. R = $CON(C_2H_5)_2$



VII

The properties of the quaternary salts obtained are summarized in Table I. The properties of the condensation products obtained with indole-3-aldehyde and those obtained from pyrrole-2-aldehyde are recorded in Tables II and III, respectively.

The ultraviolet absorption spectra of 2-(3-indolylethenyl)-1-methylpyridinium iodides were determined in acidic, basic, and neutral media. These are recorded in Table IV.

EXPERIMENTAL

Carbon and hydrogen microanalyses were performed by Weiler and Strauss, Oxford. Basic nitrogen was determined by nonaqueous titration with perchloric acid and ionic chlorine was determined by the Volhard method; both were performed in this laboratory. Micro melting points were

(1) Present address: Lasdon Foundation Research Institute, Colorado Springs, Colo.

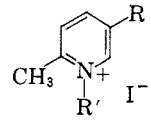
(2) A. M. Akkerman and H. Veldstra, *Rec. trav. chim.*, **73**, 629 (1954).

(3) J. Finkelstein and J. Lee, U.S. Patent **2,695,290**, November 23, 1954.

(4) A. P. Gray and W. L. Archer, *J. Am. Chem. Soc.*, **79**, 3554 (1957).

(5) J. Graf, *J. prakt. Chem.*, **133**, 19 (1932).

TABLE I

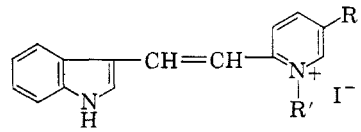


R	R′	M.P., °C.[a]	Yield, %	Formula	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
C_2H_5	CH_3	154–155	70	$C_9H_{14}IN$	41.08	41.60	5.36	5.56
$CONH_2$	CH_3	258–260	74	$C_8H_{11}IN_2O$	34.43	34.00	3.99	3.89
$CONHCH_3$	CH_3	212–214	80	$C_9H_{13}IN_2O$	37.31	37.42	4.49	4.66
$CONHC_2H_5$	CH_3	189–190	87	$C_{10}H_{15}IN_2O$	39.23	39.26	4.91	5.01
$CON(C_2H_5)_2$	CH_3	142–143	87	$C_{12}H_{19}IN_2O$	43.13	43.00	7.57	7.69
C_2H_5	C_2H_5	123–124	83	$C_{10}H_{16}IN$	43.34	43.56	5.82	5.98
$CONHC_2H_5$	C_2H_5	170–171	92	$C_{11}H_{17}IN_2O$	41.26	41.58	5.35	5.51

[a] Melting points are uncorrected

TABLE II

2-(3-INDOLYLETHENYL)-1-ALKYL-5-SUBSTITUTED PYRIDINIUM IODIDES

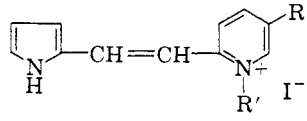


R	R′	M.P., ° C. (dec.)	Yield, %	Formula	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H	CH_3	273	68	$C_{16}H_{15}IN_2$[a]	53.06	52.64	4.17	4.41
C_2H_5	CH_3	294	41	$C_{15}H_{19}IN_2 \cdot H_2O$	54.96	55.28	5.16	5.12
$CONH_2$	CH_3	310	70	$C_{17}H_{16}IN_3O$	50.39	50.82	3.98	4.14
$CONHCH_3$	CH_3	308	78[b]	$C_{18}H_{18}IN_3O$	51.56	51.23	4.33	4.68
$CONHC_2H_5$	CH_3	308	61[b]	$C_{19}H_{20}IN_3O$	52.67	52.77	4.65	4.75
$CON(C_2H_5)_2$	CH_3	250	73	$C_{21}H_{24}IN_3O$	54.68	54.40	5.24	5.58
H	C_2H_5	285	70	$C_{17}H_{17}IN_2$	54.27	54.18	4.55	4.91
C_2H_5	C_2H_5	248	74	$C_{19}H_{23}IN_2$	56.16	56.60	5.71	5.35
$CONHC_2H_5$	C_2H_5	297	58[b]	$C_{20}H_{22}IN_3O \cdot H_2O$	51.62	51.89	5.20	5.42

[a] Akkerman and Veldstra[2] reported a melting range 260–280° with darkening; Finkelstein and Lee[3] reported m.p. 270°.
[b] Unrecrystallized yield.

TABLE III

2-(2-PYRRYLETHENYL)-1-ALKYL-5-SUBSTITUTED PYRIDINIUM IODIDES



R	R′	M.P., °C.	Yield, %	Formula	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H	CH_3	211 (dec.)	72	$C_{12}H_{13}IN_2$	46.32	45.89	4.22	4.62
C_2H_5	CH_3	196–197	72	$C_{14}H_{17}IN_2$	49.43	49.39	5.04	5.38
H	C_2H_5	181 (sl. dec.)[a]	76	$C_{13}H_{15}IN_2 \cdot H_2O$	45.62	45.80	5.19	5.18
C_2H_5	C_2H_5	286 (dec.)	75	$C_{15}H_{19}IN_2$	50.86	50.78	5.44	5.26

[a] The hydrate melted at 99–100°, then immediately resolidified.

determined on a Kofler hot stage. All melting points are uncorrected.

Starting materials. Indole-3-aldehyde was used as purchased from Aldrich Chemical Co. The 5-ethyl-2-methylpyridine obtained from Union Carbide and Carbon Chemical Corp. was fractionated before use. Pyrrole-2-aldehyde was prepared by the method of Silverstein, Ryskiewicz, and Willard.[6] The catalyst, 5% rhodium-on-alumina, was purchased from Baker and Company, Inc.

Ethyl 6-methylnicotinate. A modification of the procedure of Graf[5] was used. In each of two 10-gal. crocks containing

(6) R. M. Silverstein, E. E. Ryskiewicz, and C. Willard, *Org. Syntheses*, **36**, 74 (1956).

TABLE IV

SPECTRA OF 2-(3-INDOLYLETHENYL)-1-METHYLPYRIDINIUM IODIDE IN ACIDIC, BASIC AND NEUTRAL MEDIA

In 0.1*N* HCl				In Water				In 1.0*N* NaOH			
λ_{max} Mμ	Log ε	λ_{max} Mμ	Log ε	λ_{max} Mμ	Log ε	λ_{max} Mμ	Log ε	λ_{max} Mμ	Log ε	λ_{max} Mμ	Log ε
224	4.430	226	4.415	224	4.412	226	4.384	226	4.435	249	3.866
228	4.478	251	3.646	228	4.352	251	3.534	268	4.072	296	3.698
280	3.934	320	3.512	280	3.898	320	3.498	325	3.930	360	3.330
405	4.253	[a]		405	4.249	[a]		480	3.971	[a]	

[a] Absorbance curve dropped quickly to zero after maxima.

30 l. of water was placed 900 g. (5.69 moles) of potassium permanganate and 175.5 g. (1.45 moles) of 5-ethyl-2-methylpyridine. This solution was stirred until the reduction of the permanganate was complete (*ca.* 5 days). The manganese dioxide was filtered off and washed. The combined filtrates and washings were evaporated to a volume of 2.5 l., then allowed to stand at room temperature for 1 week. During this time the potassium pyridine-2,5-dicarboxylate separated and was removed by filtration. The solution was made slightly acidic to litmus with sulfuric acid and then evaporated to dryness.

The combined 6-methylnicotinic acid hydrosulfate and inorganic salts were powdered and dried at 110° for 24 hr. These salts were placed in a 5-l., 3-necked flask equipped with gas delivery tube and reflux condenser sealed with a drying tube. Absolute ethanol (2.5 l.) was added and a brisk stream of dry hydrogen chloride was passed through the refluxing solution for a total of 16 hr.

After reducing the volume to *ca.* 1.5 l., the esterification mixture was poured on ice and sodium carbonate. The salts and solution were extracted several times with chloroform. After drying, the chloroform solution was evaporated leaving the oily ester. Distillation at 123–125°/22 mm. gave the water-white product, n_D^{30} 1.4989. Over-all yield was 165 g. (69%).

6-Methylnicotinamide (III). The procedure of Graf[5] was followed: Ethyl 6-methylnicotinate and concentrated ammonium hydroxide were shaken together to produce the unsubstituted amide. Yield was 86%, m.p. 196–198° (from water).

N,6-Dimethylnicotinamide (IV). A solution of 10 g. (0.0605 mole) of ethyl 6-methylnicotinate and 40 ml. of 40% aqueous methylamine were allowed to react for 16 hr. The solution was evaporated to dryness providing the amide, m.p. 128–131°, yield 8.3 g. (94.5%). An analytical sample was prepared by sublimation (60°/0.02 mm.), m.p. 130–131.5°.

Anal. Calcd. for $C_8H_{10}N_2O$: C, 63.97; H, 6.71. Found: C, 63.86; H, 6.56.

N-Ethyl 6-methylnicotinamide (V). In the same manner as above, 10 g. (0.0605 mole) of ethyl 6-methylnicotinate and 40 ml. of 70% aqueous ethylamine were allowed to react. A hygroscopic compound was obtained which, when dried, amounted to 9.6 g. (96%). Purification by sublimation gave the amide m.p. 66–68°.

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.83; H, 7.35. Found: C, 65.63; H, 7.48.

N,N-Diethyl 6-methylnicotinamide (VI). A solution of 70 g. (0.424 mole) of ethyl 6-methylnicotinate and 27.7 g. (0.420 mole) of 85.2% potassium hydroxide in 200 ml. of water was refluxed for 6 hr. A means was provided whereby the ethanol produced could be removed and water added to the reaction to keep the volume constant. A quantitative yield of potassium 6-methylnicotinate was obtained by evaporating the solution to dryness and washing with ether.

Thirteen g. (0.0741 mole) of potassium 6-methylnicotinate, which had been ground to pass through a 100-mesh sieve and dried at 115°, for 6 hr., was suspended in 80 ml. of dry benzene contained in a 3-necked flask equipped with a dropping funnel, stirrer, and condenser closed with a drying tube. After the flask and contents were cooled with an ice bath a solution of 9.4 g. (0.074 mole) of oxalyl chloride in 30 ml. of dry benzene was added over a 20-min. period. The mixture was stirred for 20 min.; then the ice bath was removed and the flask and contents were allowed to come to room temperature. The reaction was stirred at room temperature for an additional hour. During this time the evolution of gases ceased.

The 6-methylnicotinyl chloride thus produced was not isolated, but 7.3 g. (0.10 mole) of diethyl amine was added over a 20-min. period. The reaction mixture was heated to reflux temperature, then allowed to cool.

The reaction mixture was acidified with dilute hydrochloric acid (5%) and the layers were separated. The aqueous layer was decolorized twice before being neutralized with 10*N* sodium hydroxide. The product was extracted with ether for 36 hr. in a liquid-liquid extractor. Removal of the dried ether provided 8.5 g. (69%) of *N,N*-diethyl 6-methylnicotinamide, b.p. 120–121°/0.4 mm.,[7] N_D^{20} 1.5225.

Substituted 2-picoline quaternary salts. These compounds, described in Table I, were all prepared by refluxing the substituted 2-picoline (0.1 to 0.2 mole) dissolved in dry benzene with an excess of methyl or ethyl iodide for 16 to 24 hr. The solid quaternary salts were filtered off and recrystallized from ethanol or ethanol–ethyl acetate.

2-(3-Indolylethenyl) 1-alkyl-5-substituted pyridinium iodides. These compounds, described in Table II, were all prepared by the condensation of indole-3-aldehyde and the appropriately substituted 2-picolinium iodides using piperidine as condensation agent. Details of the preparation of 5-(*N,N*-diethylcarbamyl)-2(3-indolylethenyl)-1-methylpyridinium iodide are given below and are illustrative of the general procedure.

A solution containing 11 g. (0.0327 mole) of 5-(*N,N*-diethyl-carbamyl)-1,2-dimethylpyridinium iodide, 4.4 g. (0.0327 mole) of indole-3-aldehyde, and 10 drops of piperidine in 250 ml. of methanol was refluxed for 20 hr. The deep red solution was concentrated to about one half its volume, then chilled for several hours.

The red crystalline product was filtered off and washed with ether. Recrystallization from methanol afforded 11 g. (73%) of the compound, m.p. 248–250° dec. An analytical sample was prepared by two additional recrystallizations.

In some cases the insolubility of the products in methanol made recrystallization difficult. In these cases only the analytical samples were recrystallized.

2-(2-Pyrrylethenyl) 1-alkyl-5-substituted pyridinium iodides. The pyrrole analogs of the above group of compounds were prepared in the same manner, substituting pyrrole-2-aldehyde in molar ratios for indole-3-aldehyde. These compounds are described in Table III. All compounds of this group were readily recrystallized from methanol.

1-Ethyl-2-(3-indolylethyl)piperidine (IIb) *and hydriodide.* Ten g. (0.0266 mole) of 1-ethyl-2-(3-iodolylethenyl)pyridinium iodide in 250 ml. of ethanol was hydrogenated over 2.0 g. of 5% rhodium-on-alumina at an initial hydrogen pressure of 50 p.s.i. for 5.5 hr. at room temperature. Re-

(7) Graf[5] obtained this compound by the reaction of 6-methylnicotinic acid azide and the amine; he reported a 57% yield (from the azide), b.p. 160–4°/12 mm.

moval of the catalyst and solvent left a thick oil. This was dried several days *in vacuo* over phosphorus pentoxide to give the solid hydriodide salt, m.m.p. 66–67°.

Anal. Calcd. for $C_{17}H_{25}N_2I$: C, 53.13; H, 6.56. Found: C, 53.04; H, 6.86.

Decomposition of the salt with sodium hydroxide resulted in the hygroscopic free base. Much of the water present was removed by codistillation with benzene. The benzene solution was decanted from a small amount of insoluble material. Removal of the solvent and extensive drying of the residue gave 5.1 g. (75%) of the white compound, m.m.p. 131.5–132°.

Anal. Calcd. for $C_{17}H_{24}N_2$: basic N, 5.58. Found: basic N, 5.63.

Hydrochloride. The hydrochloride salt was formed by passing dry hydrogen chloride through a solution of 4.0 g. (0.0156 mole) of 1-ethyl-2-(3-indolylethyl)piperidine in 75 ml. of dry ether under anhydrous conditions. As soon as the formation of the salt appeared complete the reaction flask and contents were placed in a desiccator until the compound had settled. The ether was removed by decantation and the salt washed twice with anhydrous ether. The white hygroscopic salt thus obtained was dried *in vacuo* to give 3.8 g. (90%), m.m.p. 170–173°.

Anal. Calcd. for $C_{17}H_{24}N_2$, HCl: Cl, 12.32. Found: Cl, 12.22.

5-Ethylcarbamyl-2-(3-indolylethyl)-1-methylpiperidine (IId). In the manner described above, 6.35 g. (0.0147 mole) of 5-ethylcarbamyl-2-(3-indolylethenyl)-1-methylpyridinium iodide was hydrogenated. The required hydrogen uptake was complete in 36 hr. at room temperature. After removal of the catalyst and solvent the free base was obtained by decomposition of the crude hydriodide salt with sodium hydroxide. The hygroscopic compound was dehydrated by codistillation with benzene followed by prolonged storage *in vacuo* over phosphorus pentoxide. Recrystallization, with charcoal treatment, from benzene-ligroin was accomplished by suitable protection from atmospheric moisture. After redrying, 3.5 g. (76%) of the compound was obtained, m.m.p. 138–140°.

Anal. Calcd. for $C_{19}H_{27}N_3O$: basic N, 4.54. Found: basic N, 4.40.

Hydrochloride. Observing the same precautions to exclude moisture and in the same manner as above the hydrochloride salt was prepared. Three g. (89%) of the salt was obtained from 3.0 g. (0.0098 mole) of the free base. Because even the slightest exposure to the atmosphere resulted in a hydrate, accuracy in melting point determinations was difficult. A melting point of 174–176° was obtained by filling and sealing a capillary in a dry box. This was checked by heating the compound on a hot stage 10° below its melting point for 0.5 hr. before redetermining the melting point.

Anal. Calcd. for $C_{19}H_{27}N_3O \cdot HCl$: Cl, 10.29. Found: Cl, 10.08.

5-Diethylcarbamyl-2(3-indolylethyl)-1-methylpiperidine (IIe) and hydriodide. 5-Diethylcarbamyl-2-(3-indolylethenyl)-1-methylpyridinium iodide, 10.0 g. (0.0215 mole) was hydrogenated in the same manner as above. Hydrogen uptake was steady but sluggish; 5 days at 60° were required for completion. Removal of the catalyst and solvent produced the solid hydriodide salt. An analytical sample was recrystallized from ethyl acetate, m.m.p. 110–112°.

Anal. Calcd. for $C_{21}H_{31}N_3O \cdot HI$: N, 8.95. Found: N, 8.76.

The salt was decomposed with sodium hydroxide and the resulting free base extracted into 600 ml. of benzene. This solution was dried over anhydrous calcium sulfate. Removal of the benzene by flash evaporation left an oil which slowly solidified. This was recrystallized from benzene–ethyl acetate to give 3.9 g. (57%) of the white compound, m.m.p. 213–214°.

Anal. Calcd. for $C_{21}H_{31}N_3O$: basic N, 4.11. Found: basic N, 4.08.

Tartrate. To a solution of 2.9 g. (0.00903 mole) of 5-diethylcarbamyl-2(3-indolylethyl)-1-methylpiperidine in 200 ml. of ethanol was added 0.78 *g.* (0.00045 mole) of tartaric acid. The solution was evaporated to *ca.* 20 ml., cooled, and 200 ml. of anhydrous ether was added. In contrast to previously prepared hydrochloride salts the tartrate salt was only mildly hygroscopic and easily dried *in vacuo*. Recrystallization from ethyl acetate, under anhydrous conditions, afforded 3.1 g. (82%) of the white salt, m.p. 124–126°.

Anal. Calcd. for $C_{42}H_{62}N_6O_2 \cdot C_4H_6O_6$: C, 68.97; H, 8.55. Found: C, 68.71; H, 8.91.

Absorption spectra of 2-(3-indolylethenyl)-1-methylpyridinium iodide. The absorption spectra of 2-(3-indolylethenyl)-1-methylpyridinium iodide in 1*N* sodium hydroxide, 0.1*N* hydrochloric acid, and distilled water were obtained from 220 mμ to 600 mμ of a Beckman DU spectrophotometer. Identical spectra were obtained in acidic and neutral media; in base a bathochromic shift was observed as summarized in Table IV.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MISSOURI]

Preparation of Some Simple Structural Analogs of Khellin[1,2]

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2,3,4,6-Tetramethoxy-5-ethylacetophenone, as well as several related hydroxytrimethoxyethylacetophenones have been synthesized.

The chemistry and physiological activity of khellin (I) and related compounds isolated from *Ammi visnaga* L and *Ammi majus* L have been investigated rather extensively.[4] In addition, synthetic compounds which possess some of the structural features of khellin have been reported widely. Further studies have been directed also

(1) Presented in part at the 10th Annual Kansas City, Missouri, Chemistry Conference, November 14, 1958.

(2) From the Ph.D. thesis of D. W. Rosenburg.

(3) McNeil Laboratories, Inc. Fellow, 1957–58.

(4) C. P. Huttrer and E. Dale, *Chem. Revs.*, **48**, 543 (1951).