9-Chloro- (or hydroxy)-2 and/or 7-substituted-imidazo[4,5-*f*]quinolines (1)

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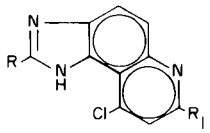
Received July 23, 1975

During the course of a synthetic program carried out in these laboratories, it was necessary to prepare a series of 9-chloro-2 and/or 7-substituted-imidazo[4,5-*f*]quinolines (Va-e) together with 9-chloroimidazo[4,5-*f*]quinoline (IVf). Although there have been numerous references concerning the preparation of imidazo[4,5-*f*]quinolines (2-8), there



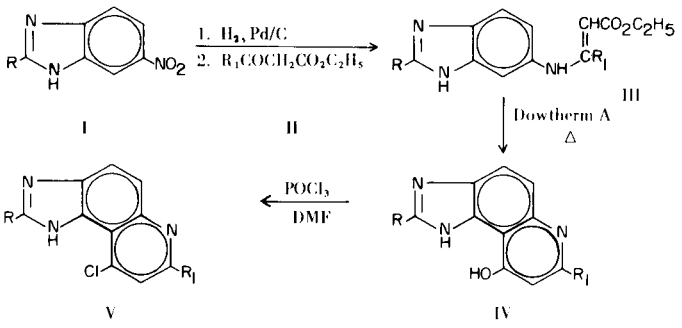
V

are only two reports of the synthesis of 9-hydroxyimidazo-[4,5-*f*]quinolines (9,10) which are the precursors for V. Five of the six 9-hydroxy compounds (IVa-e) in the present work were synthesized by the sequence shown in Scheme I. This procedure is similar to that reported by Ishiwata and Shiokawa (9) with two variations: the sequence started with 5-nitrobenzimidazoles I, and the intermediate 9-hydroxyimidazo[4,5-*f*]quinolines IV were isolated and characterized. The starting nitrobenzimidazoles I were reduced catalytically and the resulting aminobenzimidazoles, which were not isolated, were condensed with the appropriate β-ketoesters II to yield the crotonates, or cinnamates, III. Using boiling Dowtherm A (11), the esters III were cyclized to the corresponding 9-hydroxyimidazo[4,5-*f*]quinolines IV. The hydroxy compounds IV were converted smoothly to the 9-chloroimidazo[4,5-*f*] quinolines V with phosphorus oxychloride using DMF as a solvent.

The angular structures of IV and V were confirmed by an examination of their nmr spectra which showed the presence of the AB doublet of the α,β-aromatic protons with an *ortho*-coupling constant of 9 Hz. The use of nmr spectra for the determination of the angular and linear structures of imidazoquinolines has been well documented (6,8,9,10). The physical constants and data for III are summarized in Table I and those for IV and V in Tables II and III, respectively. The nmr data for IV and V are summarized in Table IV.

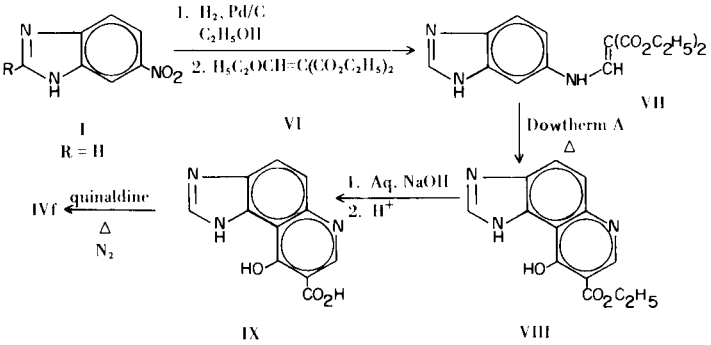
The preparation of IVf was achieved by the sequence shown in Scheme II. Catalytic reduction of 5-nitrobenz-

Scheme I



I II III IV V

Scheme II



I VI VII VIII IX

R = H

imidazole (I, R = R_1 = H) yielded 5-aminobenzimidazole which, without isolation, was condensed with diethyl ethoxymethylenemalonate (VI) to give diethyl (5-benzimidazolyl)aminomethylenemalonate (VII). Compound VII was cyclized thermally in boiling Dowtherm A to yield ethyl 9-hydroxy-1*H*-imidazo[4,5-*f*]quinoline-6-carboxylate (VIII). Hydrolysis of VIII gave the free acid IX which was converted to IVf by decarboxylation in boiling quinaldine.

EXPERIMENTAL

The prerequisite 5-nitrobenzimidazoles I were purchased (R = H) or prepared by literature procedures from 4-nitro-1,2-phenylenediamine: R = CH_3, C_6H_5 (12). Melting points were taken in open capillary tubes on a Mel-Temp melting point apparatus and are uncorrected. Nmr spectra were determined on a Varian Model A-60A spectrometer in deuterated DMSO using TMS as an internal standard.

Table I

Ethyl 3-(5-Benzimidazolylamino)crotonates (III)

Compound No.	R	R_1	M.p. °C	Yield, %	Recrys. Solvent	Empirical Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIIa	H	CH_3	160-162	69	Ethanol	$C_{13}H_{15}N_3O_2$	63.66	6.16	17.13	63.43	6.36	17.11
IIIb	H	C_2H_5	173-175	70	Ethanol	$C_{14}H_{17}N_3O_2$	64.84	6.61	16.21	64.66	6.52	16.27
IIIc	H	C_6H_5	203-205	60	Ethanol	$C_{18}H_{17}N_3O_2$	70.34	5.58	13.67	70.37	5.76	13.68
IIId	CH_3	CH_3	142-145	52	aq. Ethanol	$C_{14}H_{17}N_3O_2$	64.84	6.61	16.21	64.86	6.58	16.28
IIIe	C_6H_5	CH_3	150-152	87	Benzene	$C_{19}H_{19}N_3O_2$	71.00	5.96	13.08	70.99	5.84	13.26

Table II

9-Hydroxyimidazo[4,5-*f*]quinolines (IV)

Compound No.	R	R_1	M.p., °C	Yield, %	Recrys. Solvent	Empirical Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IVa	H	CH_3	345-347	91	DMF	$C_{11}H_9N_3O$	66.32	4.55	21.10	66.19	4.78	20.94
IVb	H	C_2H_5	334-335	84	DMF	$C_{12}H_{11}N_3O$	67.59	5.20	19.71	67.43	5.02	19.55
IVc	H	C_6H_5	320-322	45	DMF	$C_{16}H_{11}N_3O$	73.55	4.24	16.08	73.35	4.44	16.03
IVd	CH_3	CH_3	>400	81	DMF	$C_{12}H_{11}N_3O$	67.59	5.20	19.71	67.33	5.30	19.71
IVe	C_6H_5	CH_3	332-336 dec.	70	DMF	$C_{17}H_{13}N_3O$	74.16	4.76	15.27	73.79	4.68	15.27
IVf	H	H	366-368	89	Ethanol	$C_{10}H_7N_3O$	64.86	3.81	22.69	64.88	3.82	22.69

Table III

9-Chloroimidazo[4,5-*f*]quinolines (V)

Compound No.	R	R_1	M.p., °C	Yield, %	Recrys. Solvent	Empirical Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Va	H	CH_3	>300	96	Aq. Ethanol	$C_{11}H_8ClN_3$	60.70	3.70	19.31	60.68	4.01	18.97
Vb	H	C_2H_5	189-193	85	Ethanol	$C_{12}H_{10}ClN_3$	62.21	4.35	18.14	62.18	4.36	18.12
Vc	H	C_6H_5	>230 dec.	51	Ethanol	$C_{16}H_{10}ClN_3$	68.70	3.60	15.02	69.04	3.63	15.07
Vd	CH_3	CH_3	>400 dec.	57	Methanol	$C_{12}H_{10}ClN_3$	62.21	4.35	18.14	62.06	4.34	18.07
Ve	C_6H_5	CH_3	175-179 dec.	44	Methanol	$C_{17}H_{12}ClN_3$	69.51	4.12	14.31	69.38	4.27	14.32
Vf	H	H	<400 dec.	84	Methanol	$C_{10}H_6ClN_3$	58.98	2,97	20.64	58.99	2.99	20.69

Ethyl 3-[5-(2-Substituted-benzimidazolyl)amino]crotonate (III).

The general procedure can be exemplified by the preparation of ethyl 3-[5-(benzimidazolyl)amino]crotonate (IIIa). A sample of 5-nitrobenzimidazole (I, R = H) (82 g., 0.5 mole) was reduced in a Parr hydrogenation apparatus in absolute ethanol in the presence of 5% Pd/C catalyst (4 g. containing 50% water) at 40 psi initial pressure. The reaction stopped after absorption of 100% of the calculated amount of hydrogen. After removal of the catalyst by filtration, ethyl acetoacetate (II, $R_1 = CH_3$) (65 g., 0.5 mole) was added to the filtrate together with anhydrous calcium sulfate (20 g.) and acetic acid (0.5 ml.). After heating at reflux for 2 hours, the mixture was filtered and the filtrate was concentrated *in vacuo* to afford a solid. The crude material was washed with fresh absolute ethanol and air-dried to yield IIIa (84 g.).

9-Hydroxy-2 and/or 7-substituted-imidazo[4,5-*f*]quinolines (IV).

The preparation of 9-hydroxy-7-methylimidazo[4,5-*f*]quinoline (IVa) will demonstrate the general procedure. Compound IIIa (40 g., 0.16 mole) was added in small portions to boiling Dowtherm A (800 ml.). After the addition, the mixture was boiled for an additional 6 minutes and then cooled. The separated product was collected by filtration, washed with Dowtherm A and acetone, and air-dried to yield IVa (29 g.).

9-Chloro-2 and/or 7-substituted-imidazo[4,5-*f*]quinolines (V).

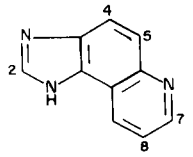
The chlorination of IVa will serve as a general example for the preparation of V. To a stirred suspension of IVa (400 g., 2.0 moles) in phosphorus oxychloride (3000 g., 20 moles) was added DMF (1800 ml.) dropwise over a period of 2 hours. The temperature was permitted to rise to 85° and the mixture was then cooled to 40° with a cold water bath. Removal of the water bath permitted the temperature to rise to 55°, after which the mixture was stirred overnight. The viscous mixture was poured onto ice (10 kg). The resulting solution was treated with charcoal and filtered. The filtrate was neutralized to *p*H 6 with 20% sodium hydroxide solution with the addition of ice as needed for cooling. The precipitate was collected, washed with water, and dried at 80° to yield 9-chloro-7-methylimidazo[4,5-*f*]quinoline (Va) (419 g.).

Diethyl [(5-Benzimidazolyl)amino]methylenemalonate (VII).

To a solution of I (R = R_1 = H) (82 g., 0.5 mole) in absolute

Table IV

NMR Spectra (a) of IV and V



Compound No.	C(2)-H	C(4)-H	C(5)-H	C(7)-H	C(8)-H
IVa	8.23	7.45 (d) J = 9	8.01 (d) J = 9	---	6.15
IVb	8.26	7.48 (d) J = 9	8.05 (d) J = 9	---	6.20
IVc	8.30	7.71 (d) J = 9	8.10 (d) J = 9	---	6.61
IVd	---	7.43 (d) J = 9	7.75 (d) J = 9	---	6.15
IVe	---	7.46 (d) J = 9	8.06 (d) J = 9	---	6.15
IVf	8.33	7.53 (d) J = 9	8.13 (d) J = 9	6.37 (d) J = 7	8.07 (d) J = 7
Va	8.46	7.86 (d) J = 9	8.16 (d) J = 9	---	7.66
Vb	8.46	7.86 (d) J = 9	8.06 (d) J = 9	---	7.68
Vc	8.51	8.00 (d) J = 9	8.21 (d) J = 9	---	7.51
Vd	---	7.70 (d) J = 9	8.01 (d) J = 9	---	7.60
Ve	---	7.85 (d) J = 9	8.33 (d) J = 9	---	---
Vf	8.55	7.96 (d) J = 9	8.23 (d) J = 9	7.80 (d) J = 5	8.85 (d) J = 5
IX (b)	8.25	7.57 (d) J = 9	7.90 (d) J = 9	8.79	---

(a) The chemical shifts are reported as ppm (δ); J = Hz. (b) Spectrum was obtained from a solution of compound in deuterium oxide and sodium deuteroxide.

ethanol (1000 ml.) was added 5% palladium-charcoal catalyst (5 g. containing 50% water). The mixture was shaken under hydrogen until the reaction stopped after a pressure drop of 97% of the calculated amount - about 75 minutes. After removal of the catalyst by filtration, diethyl ethoxymethylenemalonate (VI) (108 g., 0.5 mole) was added to the filtrate. The solution was distilled until about one-half of the solvent had been removed. The residue was cooled and the crystallized product was collected. The crude material was washed with cold 25% aq. ethanol and air-dried to yield VII (125 g., 83%), m.p. 188-189°. An analytical sample was prepared by recrystallization from absolute ethanol, m.p. 192-194°.

Anal. Calcd. for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.65; N, 13.86. Found: C, 59.61; H, 5.89; N, 14.02.

Ethyl 9-Hydroxy-1H-imidazo[4,5-*f*]quinoline-8-carboxylate (VIII).

The malonate VII (50 g., 0.16 mole) was added in small portions to boiling Dowtherm A (500 ml.) over a 5-minute period. The reaction mixture was cooled and filtered. The crude solid material was extracted with boiling absolute ethanol to yield VIII (22 g., 52%), m.p. 315-316°. An analytical sample was prepared by recrystallization from 1-methyl-2-pyrrolidinone, m.p. 315-316°.

Anal. Calcd. for $C_{13}H_{11}N_3O_3$: C, 60.69; H, 4.31; N, 16.34. Found: C, 60.29; H, 4.49; N, 16.02.

9-Hydroxyimidazo[4,5-*f*]quinoline-8-carboxylic Acid (IX).

A mixture of VIII (356 g., 1.38 mole) and 2*N* sodium hydroxide solution (3000 ml.) was heated at reflux for 3 hours. The cooled solution was stirred for one hour with charcoal and filtered. The filtrate was acidified with concentrated hydrochloric acid (509 ml.) and the precipitated product collected. The crude material was recrystallized from DMF (charcoal) to yield IX (284 g., 90%), m.p. 310° dec. An analytical sample was prepared by recrystallization from DMF, m.p. 310° dec.

Anal. Calcd. for $C_{11}H_7N_3O_3$: C, 57.64; H, 3.08; N, 18.34. Found: C, 57.65; H, 3.06; N, 18.12.

9-Hydroxyimidazo[4,5-*f*]quinoline (IVf).

A mixture of IX (254 g., 1.1 moles) and quinaldine (1400 ml.) was heated at reflux for 9 hours while sweeping the system with nitrogen. The brown solid which formed was collected by filtration, washed with benzene and air-dried to yield IVf (183 g., 89%), m.p. 364-396°. An analytical sample was prepared by suspending the material in dilute hydrochloric acid and filtering. The filtrate was cooled and neutralized to pH 8 by the addition of concentrated ammonium hydroxide. The product was collected, washed with water and dried at 100°.

Acknowledgment.

The authors wish to thank Mr. Mark Rice and Mr. Ronald Storrin for the preparation of chemical intermediates and technical assistance, Mr. Grant Gustin, Mr. Marvin Tefft and Mr. Warren Smith for microanalyses, and Mrs. Patricia Curtis and Mrs. Connie Lloyd for determination of the nmr spectra.

REFERENCES

(1) These compounds have been covered by three patent applications filed June 3, 1973 which resulted in U.S. Patent Nos. 3,868,378 (Feb. 25, 1975) and 3,878,206 (April 15, 1975) and a third patent pending.

(2) K. Fries, E. Modrow, B. Raeke and K. Weber, *Ann. Chem.*, 454, 121 (1927).

(3) R. Weidenhagen and V. Weeden, *Ber.*, 71B, 2347 (1938).

(4) B. I. Khristich and A. M. Simonov, *Khim. Geterotsikl. Soedin.*, 2, 611 (1966).

(5) A. M. Simonov, B. I. Khristich, and V. G. Polundo, *ibid.*, 3, 927 (1967).

(6) S. Ishiwata and Y. Shiokawa, *Chem. Pharm. Bull.*, 17, 1153 (1969).

(7) M. Kamel, S. Sherif, R. M. Issa, and F. I. Abd-El-Hay, *Tetrahedron*, 29, 221 (1973).

(8) M. Gandino and A. R. Katritzky, *Ann. Chim. (Rome)*, 60, 462 (1970).

(9) S. Ishiwata and Y. Shiokawa, *Chem. Pharm. Bull.*, 17, 2455 (1969).

(10) E. B. Mullock, R. Searby, and H. Suschitzky, *J. Chem. Soc. (C)*, 1970, 829.

(11) Dowtherm A is the trademark of Dow Chemical Co. for the eutectic mixture of diphenyl ether and biphenyl.

(12) D. G. Bapat and M. V. Shirsat, *Indian J. Chem.*, 3, 81 (1965).