4-Substituted-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazines

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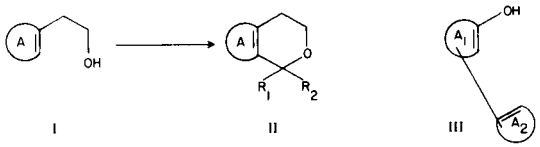
The condensations of 1-(2-hydroxyphenyl)pyrroles with a variety of carbonyl compounds are shown to give new 4-substituted-4*H*-4-methylpyrrolo[2,1-*c*][1,4]benzoxazines. Some of the products were further functionalized. The ir, uv, and pmr spectra of the title heterocyclic system are discussed. Reaction of 1-(2-hydroxyphenyl)pyrrole with dimethyl acetylenedicarboxylate yielded dimethyl 3-(2-hydroxyanilino)phthalate; a mechanistic rationale which accounts for the result involves a rearrangement of the hypothetical Diels-Alder adduct.

J. Heterocyclic Chem., 13, 311 (1976).

The preceding papers from our Laboratories (1,2,3) described the condensation of alcohols I (A = aromatic or heteroaromatic moiety) with carbonyl compounds R_1-CO-R_2 to give a number of novel pyrano-fused ring systems II.

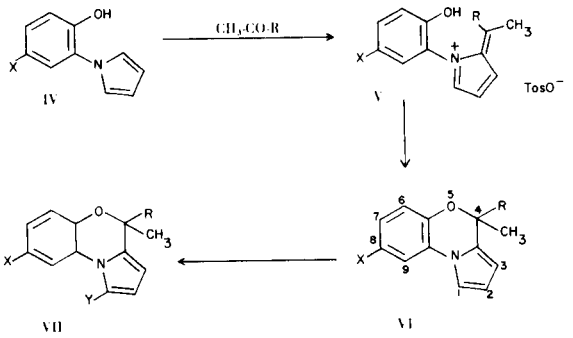


I II III

This acid-catalyzed condensation proved to be of wide applicability, and some of the appropriately substituted products (R_1 = alkyl, R_2 = CH_2-COOH or $(CH_2)_n$-N<) exhibited interesting biological properties (2,3,4). These results prompted us to examine an analogous reaction with phenolic compounds of type III. As a model, we chose the heteroaromatic system III where A_1 is a benzene ring and A_2 represents a pyrrole ring. Thus, the condensation of IV (X = H, Cl, or NO_2) with a variety of carbonyl components proceeded relatively smoothly in the presence of *p*-toluenesulfonic acid (*p*-TSA) and afforded a series of 4-substituted-4*H*-4-methylpyrrolo[2,1-*c*][1,4]benzoxazines VI (Scheme 1).

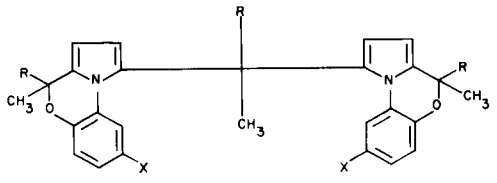
The proposed intermediacy of azafulvenium salts V is supported by the following facts: a) transient formation of precipitates has been observed in hot benzene solutions of IV, carbonyl compounds and *p*-TSA. b) the condensation is inhibited by electron-withdrawing substituents in the benzene ring, c) under the conditions for the Hofmann elimination, Artico *et al.* (5) treated 1-(2-hydroxyphenyl)-2-(dimethylaminomethyl)pyrrole methiodide with sodium ethoxide to obtain a mixture of 4*H*-pyrrolo[2,1-*c*][1,4]-benzoxazine and 1-(2-hydroxyphenyl)-2-(ethoxymethyl)-pyrrole.

Scheme I



IV V VII VI

The cyclization products VI were obtained in good yields, however, it should be noted that a side reaction also occurred, and by-products VIII were isolated in several cases. The formation of VIII can be minimized by heating first the pyrrolic component IV with *p*-TSA in benzene, and adding the carbonyl component CH_3-CO-R thereafter.



VIII

4*H*-Pyrrolo[2,1-*c*][1,4]benzoxazines studied are listed in Table I. The esters VIe-h were routinely hydrolyzed to the carboxylic acids VIj-m, and the corresponding amides VIn-s were prepared using mild conditions provided by the mixed anhydride procedure; reduction by means of

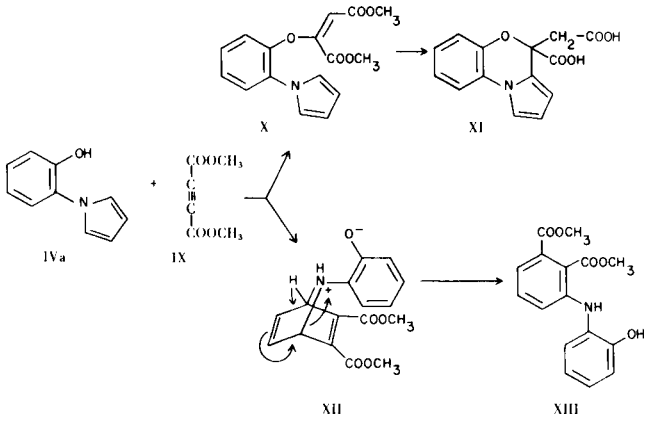
lithium aluminium hydride afforded aminoalkyl derivatives VIt-w. Some of the tricyclic compounds VI were further functionalized by electrophilic substitution which took place preferentially (6) in position 1 (Scheme I). The products VII were more stable in acidic media and towards air oxidation than the parent compounds VI. Chlorination with sulfuryl chloride afforded VIIa-b, and nitration with a nitric acid-acetic anhydride gave VIIc. A Friedel-Crafts type acylation using trifluoroacetic anhydride led to VIId-e. The Mannich condensation readily provided 1-*t*-aminomethyl derivatives VIIf-g.

The ir spectra of VIa-w and VIIa-b display a strong and distinct absorption band at 1515-1500 cm^{-1} (chloroform or nujol) which is assigned to ring-stretching modes of the pyrrole nucleus. The frequency is somewhat depressed (1495-1490 cm^{-1}) in the spectra of VIIc-g. This characteristic band does not interfere with the nitro-group absorption at 1525-1520 cm^{-1} (VIi and VIIb-e). The uv spectra of 4*H*-pyrrolo[2,1-*c*][1,4]benzoxazines exhibit a consistent pattern; the unsubstituted compounds VI (X = Y = H) give an absorption of high extinction coefficient 21,700-24,900 at 217-218 nm (methanol), another band at 264-265 nm (ϵ 8,600-11,000), and finally an absorption maximum at 291-293 nm (ϵ 6,500-7,500).

An examination of the pmr spectra has shown that chemical shifts of the protons on the pyrrole ring cover a narrow range of δ values which are essentially unaffected by substitution on the benzene ring. For the majority of compounds VI, the 3-H protons gave a pair of doublets at δ 5.95-6.09 ($J_{2,3}$ = 3.0-3.5 Hz, $J_{1,3}$ = 1.5 Hz), and the signals caused by the 2-H protons appeared as triplets at δ 6.25-6.38 ($J_{1,2} = J_{2,3}$ = 3.0-3.5 Hz). In some cases, the 3-H signal was shifted downfield and the spectra displayed a multiplet at δ 6.26-6.36 integrating for two protons (VIe,j,k,p,t,u,w). The signals due to 1-H protons were obscured by the main aromatic envelope. The 2-H and 3-H protons constitute an AB system in 1-substituted derivatives VII, and accordingly, singlet (VIIa), doublet (VIId-e), or more typically two symmetrical doublets (VIIb,f,g) were observed at δ 5.9-6.9, $0 \leq J_{AB} \leq 5$ Hz. Aromatic protons 9-H were deshielded by electronegative substituents at position 1 and/or 8. This effect (*cf.* reference 6) was intensified in the nitro-derivative VIIb where the resonance signal for H-9 occurred at δ 9.0.

As an extension of our work, we have investigated the reaction of 1-(2-hydroxyphenyl)pyrrole IVa (X = H) with dimethyl acetylenedicarboxylate IX. In the presence of Dabco catalyst, the mixture of IVa and IX in boiling ether yielded the enol-ether X (Scheme 2); cyclization and concomitant hydrolysis (X → XI) was effected by aqueous sodium hydroxide. A surprisingly facile rearrangement to afford XIII was observed on performing the same addition (IVa + IX) under neutral conditions in boiling dioxane.

Scheme 2



The formation of XIII probably proceeds *via* the Diels-Alder adduct XII. The dipolar structure of this 7-azanorbornadiene derivative may trigger the isomerization process which stabilizes the six π-electron system. The fact that we could not isolate XII is not surprising since 7-phenyl-7-azanorbornadienes of this type were found thermally unstable in previous studies (7,9). An analogous rearrangement of dimethyl 7-carbethoxy-7-azabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate upon treatment with aluminum chloride was reported by Bansal and coworkers in 1970 (8). Recently, dimethyl 3-(dimethylamino)phthalate was generated by the thermolysis of dimethyl 7,7-dimethyl-7-azoniabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate-tetrafluoroborate (9). It appears reasonable to conclude that the acidity of the phenolic function in XII is sufficient to initiate the illustrated mechanism (Scheme 2).

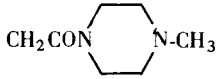
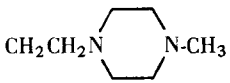
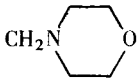
EXPERIMENTAL

All melting points are uncorrected. Routine ir spectra were recorded on a Perkin-Elmer 700 spectrometer and the expanded ir spectra were run on a Perkin-Elmer 225 spectrometer. A Zeiss DMR 21 spectrophotometer was used to measure the uv spectra. The pmr spectra were determined on a Varian A-60A instrument and chemical shifts are reported in units of δ (ppm) downfield from TMS as an internal standard. Mass spectra were obtained on a LKB 9000S mass spectrometer. The procedures are illustrated by the representative preparations.

1-(2-Hydroxy-5-chlorophenyl)pyrrole (IVb, X = Cl).

A mixture of 5-chloro-2-hydroxyaniline (7.15 g., 0.05 mole), 2,5-dimethoxytetrahydrofuran (6.6 g., 0.05 mole), dioxane (50 ml.), and acetic acid (30 ml.) was heated to reflux for 4 hours. The volatiles were removed with a rotavapor, and the residue was taken between ether (100 ml.) and 3% aqueous sodium hydroxide (150 ml.). The brownish aqueous phase was acidified (*p*H adjusted to 4) with hydrochloric acid and extracted with chloroform. The combined extracts were concentrated, and passed through a chromatographic column of silica gel to give 5.1 g. (53%) of the title compound (homogeneous on tlc); ir (chloroform): 3530, 3200 (broad), and 1500 cm^{-1}; pmr (deuteriochloroform): 5.40 (broad,

Table I

	R	X	Y	M.p. °C	Formula	Analysis Calcd. % C	H	N	Cl	Found % C	H	N	Cl
VIa	CH_3	H	H	38-40	$C_{13}H_{13}NO$	78.36	6.58	7.03		78.10	6.39	6.95	
b	CH_3	Cl	H	76-78	$C_{13}H_{12}ClNO$	66.81	5.17	5.99	15.17	66.62	5.15	6.03	15.09
c	CH_2OH	H	H	---									
d	$CH_2NHCOCH_3$	H	H	---									
e	$COOC_2H_5$	H	H	---									
f	$COOC_2H_5$	Cl	H	---									
g	$CH_2COOC_2H_5$	H	H	---									
h	$CH_2COOC_2H_5$	Cl	H	---									
i	CH_2COOCH_3	NO_2	H	132-133	$C_{15}H_{14}N_2O_2$	59.60	4.67	9.27		59.40	4.65	9.08	
j	COOH	H	H	143-144	$C_{13}H_{11}NO_3$	68.11	4.84	6.11		68.14	4.86	6.13	
k	COOH	Cl	H	153-154	$C_{13}H_{10}ClNO_3$	59.21	3.82	5.31	13.45	59.13	3.91	5.26	13.36
l	CH_2COOH	H	H	121-122	$C_{14}H_{13}NO_3$	69.12	5.39	5.76		68.92	5.49	5.70	
m	CH_2COOH	Cl	H	---									
n	CH_2CONH_2	H	H	---									
o	$CON(CH_3)_2$	H	H	---									
p	$CON(CH_3)_2$	Cl	H	118-119	$C_{15}H_{15}ClN_2O_2$	61.96	5.20	9.63		61.86	5.18	9.43	
q	$CH_2CON(CH_3)_2$	H	H	---									
r	$CH_2CON(CH_3)_2$	Cl	H	---									
s		H	H	---									
t	$CH_2N(CH_3)_2$	H	H	242-243 (a)	$C_{15}H_{18}N_2O\cdot HCl$	64.62	6.87	10.05	12.72	64.62	6.90	9.92	12.69
u	$CH_2N(CH_3)_2$	Cl	H	238-239 (a)	$C_{15}H_{17}ClN_2O\cdot HCl$	57.51	5.79	8.94	22.64	57.64	5.85	8.88	22.59
v	$CH_2CH_2N(CH_3)_2$	H	H	253-255 (a)	$C_{16}H_{20}N_2O\cdot HCl$	65.63	7.23	9.57	12.11	65.15	7.27	9.44	11.96
w		H	H	253-254 (a)	$C_{19}H_{25}N_3O\cdot HCl$	59.37	7.08	10.93	18.45	59.43	7.16	10.83	18.75
VIIa	$CH_2N(CH_3)_2$	H	Cl	212-214 (a)	$C_{15}H_{17}ClN_2O\cdot HCl$	57.51	5.79	8.94	22.64	57.74	5.80	8.93	22.38
b	CH_2COOCH_3	NO_2	Cl	124-125	$C_{15}H_{13}ClN_2O_5$	53.50	3.89	8.32	10.53	53.39	3.86	8.10	10.81
c	$CH_2N(CH_3)_2$	H	NO_2	247-248 (a)	$C_{15}H_{17}N_3O_3\cdot HCl$			12.97	10.95			13.06	11.20
d	$CH_2CON(CH_3)_2$	H	F_3CCO	81-83	$C_{18}H_{17}F_3N_2O_3$	59.01	4.68	7.64		58.68	4.81	7.50	
e	$CH_2N(CH_3)_2$	H	F_3CCO	122-124 (a)	$C_{17}H_{17}F_3N_2O_2\cdot HCl\cdot 2H_2O$			6.81	8.63			6.81	8.45
f	CH_3	H	$CH_2N(CH_3)_2$	188-189 (a)	$C_{16}H_{20}N_2O\cdot HCl$	65.63	7.23	9.57	12.11	65.53	7.36	9.39	11.98
g	CH_3	H		149-150 (b)	$C_{18}H_{22}N_2O_2\cdot C_4H_4O_4$	63.75	6.32	6.76		63.98	6;39	6.69	

(a) hydrochloride. (b) maleate. The oily intermediates VIc-h, m-o, q-r were purified chromatographically and shown to be homogeneous by tlc analyses; the ir and/or pmr spectra were compatible with the assigned structures; compound VIs was contaminated with ~10% *N*-methylpiperazine (see Experimental part).

1H, OH), 6.37 (t, J = 2 Hz, 2H, β protons of pyrrole), 6.82 (t, J = 2 Hz, 2H, α protons of pyrrole).

1-(2-Hydroxy-5-nitrophenyl)pyrrole (IVc, X = NO_2).

Similarly, this compound was obtained in 70% yield; m.p. 80-81° (ether-hexane); ir (chloroform): 3515, 3100 (broad), 1595, 1525, and 1505 cm^{-1}; pmr (deuteriochloroform): 6.10 (broad, 1H, OH), 6.40 (m, 2H, β protons of pyrrole), 6.90 (m, 2H, α protons of pyrrole), and 3 aromatic protons 7.15 (d, J_o = 9.5 Hz), doublet of doublets centered at 8.18 (J_o = 9.5 Hz, J_m = 3 Hz), 8.18 (d, J_m = 3 Hz).

Anal. Calcd. for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.70; H, 3.91; N, 13.84.

1-(2-Hydroxyphenyl)pyrrole (IVa, X = H).

This compound was obtained in a yield of 75%; m.p. 52-54°; lit. (5) m.p. 45-47°, lit. (6) m.p. 53-54°; ir (chloroform): 3530, 1600, and 1505 cm^{-1}; pmr (deuteriochloroform): 5.30 (broad, 1H, OH), 6.36 (t, J = 2 Hz, 2H, β protons of pyrrole), 6.84 (t, J = 2 Hz, 2H, α protons of pyrrole).

4,4-Dimethyl-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (VIa).

A solution of IVa (1.1 g.) and *p*-toluenesulfonic acid monohydrate (0.11 g.) in 70 ml. of dry benzene was refluxed under the Dean-Stark water separator for 20 minutes. Then, 10 ml. of acetone was added, and the reflux conditions maintained for 15 hours. After cooling, the reaction mixture was washed with 10% sodium bicarbonate, dried over magnesium sulfate, filtered, and evaporated. The residual oil was chromatographed on silica gel, using chloroform-benzene (1:1) mixture as eluent. The front fraction (1 g., 73%) was homogeneous on tlc, and solidified; m.p. 38-40° (pentane); ir (chloroform): 1600, 1510, and 1145 cm^{-1}; pmr (deuteriochloroform): 1.59 (s, 6H, CH_3), two doublets centered at 5.96 (J_{23} = 3.5 Hz, J_{13} = 1.5 Hz, 1H, 3-H), a triplet with fine aplitting at 6.26 (J = 3.5 Hz, 1H, 2-H).

A similar reaction of IVb with acetone gave VIb which was purified by chromatography on silica gel, elution with benzene-hexane (2:3) mixture, yield 47%, m.p. 76-78° (cyclohexane).

4-Hydroxymethyl-4*H*-4-methylpyrrolo[2,1-*c*][1,4]benzoxazine (VIc).

A mixture of IVa (477 mg.), acetoxyacetone (348 mg.), *p*-toluenesulfonic acid monohydrate (50 mg.) and benzene (60 ml.) was refluxed under the Dean-Stark trap for 2 hours. An additional portion of acetoxyacetone (174 mg.) was added, and the reflux was continued for 12 hours. The reaction mixture was evaporated to dryness *in vacuo*, the residue was dissolved in 50 ml. of methanol and 1 ml. of 50% potassium hydroxide was added. The resultant solution was stirred at room temperature overnight, methanol was removed with rotavapor, and the residue partitioned between water and chloroform. The organic phase was concentrated, and passed through a small column of silica gel (set in chloroform) to give 300 mg. (47%) of the title compound; ir (chloroform): 3575 and 1510 cm^{-1}; pmr (deuteriochloroform): 1.64 (s, 3H, CH_3), 1.95 (broad s, 1H, OH), 3.60 and 3.85 (two doublets, J_{gem} = 12 Hz, 2H, CH_2-O), two doublets centered at 6.08 (J_{23} = 3.5 Hz, J_{13} = 1.5 Hz, 1H, 3-H), a triplet with fine splitting at 6.34 (J = 3.5 Hz, 1H, 2-H).

Preparation of 4*H*-4-Methylpyrrolo[2,1-*c*][1,4]benzoxazines (VId-i).

A solution of IVa (5 g.), ethyl acetoacetate (4.3 g.), and *p*-toluenesulfonic acid monohydrate (0.5 g.) in 900 ml. of benzene was refluxed under the Dean-Stark trap for 18 hours. The reaction mixture was filtered and washed successively with 10% sodium bicarbonate, water, and saturated brine solution. Removal of the benzene *in vacuo* afforded an oil which was chromatographed on a column of silica gel packed in chloroform. There was obtained 6.9 g. (81%) of VIg; ir (chloroform): 1725, 1600, and 1505 cm^{-1}; pmr (deuteriochloroform): 1.18 (t, J = 7 Hz, 3H, CH_3 of ethyl), 1.88 (s, 3H, CH_3), 2.79 (s, 2H, CH_2-CO), 4.05 (q, J = 7 Hz, 2H, CH_2 of ethyl), two doublets centered at 6.03 (J_{23} = 3 Hz, J_{13} = 1.5 Hz, 1H, 3-H), 6.30 (t, J = 3 Hz, 1H, 2-H), 6.9-7.5 (m, 5H, 1-H and aromatic protons).

Using this procedure, condensation of IVb with ethyl acetoacetate afforded 34% of VIh.

Similarly, condensation of IVc with methyl acetoacetate provided VIi: yield 59%; m.p. 132-133° (benzene-hexane); ir (chloroform): 1730, 1525, and 1505 cm^{-1}; pmr (deuteriochloroform): 1.89 (s, 3H, CH_3), 2.85 (s, 2H, CH_2-CO), 3.63 (s, 3H, CH_3-O), two doublets centered at 6.14 (J_{23} = 3.5 Hz, J_{13} = 1.5 Hz, 1H, 3-H), 6.40 (t, J = 3.5 Hz, 1H, 2-H), 7.15 (d, J_o = 9 Hz, 1H, 6-H), two doublets centered at 7.27 (J_{12} = 3.5 Hz, J_{13} = 1.5 Hz, 1H, 1-H), two doublets centered at 8.04 (J_o = 9 Hz, J_m = 2.5 Hz, 1H, 7-H), 8.26 (d, J_m = 2.5 Hz, 1H, 9-H).

In the same manner but replacing benzene with toluene, IVa was condensed with acetamidoacetone to give 50% of VId: pmr (DMSO-d_6): 1.48 (s, 3H, CH_3), 1.78 (s, 3H, CH_3-CO), 3.42 (d, J = 6 Hz, 2H, CH_2-N), two doublets centered at 6.06 (J_{23} = 3.5 Hz, J_{13} = 1.5 Hz, 1H, 3-H), 6.25 (t, J = 3.5 Hz, 1H, 2-H), 7.0-7.5 (m, 5H, 1-H and aromatic protons), 7.85 (broad, 1H, NH).

To prepare VIe-f, the above method was followed except that reaction time was reduced to 1-2 hours. Thus, condensation of ethyl pyruvate with IVa in benzene afforded VIe (57%), and IVb was converted to VIf (35%).

Carboxylic Acids (VIj-m).

A stirred solution of the ester VIe (24 g.) in methanol (400 ml.) and 10% aqueous sodium hydroxide (100 ml.) was refluxed for 2 hours. Methanol was removed under reduced pressure, the remaining slurry dissolved in water, and washed with ether. The aqueous part was carefully acidified with diluted hydrochloric acid, and extracted with chloroform. The combined extracts were dried over magnesium sulfate, filtered, and evaporated. The product, VIj, was crystallized from benzene-hexane (1:1), m.p. 143-144°, yield 14.5 g. (68%): ir (chloroform): 2900-2500, 1725, 1600, and 1510 cm^{-1}; pmr (deuteriochloroform): 1.92 (s, 3H, CH_3), 6.28 (m, 2H, 2-H and 3-H), 6.9-7.4 (m, 5H, 1-H and aromatic protons), 9.0 (s, 1H, COOH).

The following acids were similarly prepared: VIk, yield 52%, m.p. 153-154° (ether-hexane); ir (chloroform): 2900-2500, 1725, and 1510 cm^{-1}. VIl, yield 65%, m.p. 121-122° (ether-hexane); ir (chloroform): 2900-2500, 1700, and 1500 cm^{-1}; pmr (deuteriochloroform): 1.87 (s, 3H, CH_3), 2.72 and 2.98 (two doublets, J_{gem} = 14.5 Hz, 2H, CH_2-CO), two doublets centered at 6.08 (J_{23} = 3.5 Hz, J_{13} = 1.5 Hz, 1H, 3-H), 6.31 (t, J = 3.5 Hz, 1H, 2-H), 7.0-7.4 (m, 5H, 1-H and aromatic protons), 10.7 (broad, 1H, COOH). VIm; yield 37%; ir (chloroform): 2900-2500, 1728, and 1500 cm^{-1}; the sample crystallized from benzene-hexane was found to contain benzene of solvation which was difficult to remove entirely.

Amides VIn-s.

A solution of VII (1.7 g.) in dry tetrahydrofuran (40 ml.) was treated with triethylamine (2.25 g.) at -5°. Then, ethyl chloroformate (2.5 g. in 10 ml. of tetrahydrofuran) was added from a dropping funnel, and the resultant slurry was stirred at -5° for 2 hours. The mixed anhydride thus formed *in situ* was decomposed

by addition of concentrated ammonium hydroxide (40 ml.), and the reaction mixture was stirred at ambient temperature for 2 hours. Tetrahydrofuran was removed *in vacuo*, the residue was diluted with water, and extracted with chloroform. Customary work-up of the organic phase gave 1.7 g. of the crude amide VIn which was purified chromatographically; yield 1.4 g. (86%); ir (chloroform): 3510, 3390. 1675, 1600, 1580, and 1510 cm^{-1}; pmr (deuteriochloroform): 1.72 (s, 3H, CH_3), 2.68 and 2.99 (two doublets, J_{gem} = 15 Hz, 2H, CH_2-CO), 6.00 (broad, 2H, NH_2).

An analogous procedure was employed to prepare the following amides: VIo, yield 62%; ir (chloroform): 1640 cm^{-1}; pmr (deuteriochloroform): 1.78 (s, 3H, CH_3), 3.0 (s, 6H, N-CH_3). VIp, m.p. 118-119° (ether-hexane), yield 56%; ir (chloroform): 1640 cm^{-1}; pmr (deuteriochloroform): 1.83 (s, 3H, CH_3), 2.21 (broad singlet, 6H, CH_3-N). VIq, yield 58%; ir (chloroform): 1635 cm^{-1}; pmr (deuteriochloroform): 1.92 (s. 3H. CH_3), 2.55 and 2.83 (singlets, 6H, CH_3-N), 2.81 and 3.05 (two doublets, J_{gem} = 13 Hz, 2H, CH_2-CO). VIr, yield 39%; ir (chloroform): 1680 and 1630 cm^{-1}. VIs, yield 60%; this compound was contaminated with ~ 10% of *N*-methylpiperazine.

Preparation of Amines VIt-w.

To a stirred slurry of lithium aluminum hydride (3 g.) in 100 ml. of dry ether was added dropwise a solution of the amide (VIo-q or VIs, 3 g.) in 100 ml. of the same solvent. The reaction mixture was stirred at room temperature overnight, and decomposed by successive addition of water (3 ml.), 15% solution hydroxide (3 ml.), and water (9 ml.). The precipitate was filtered off, the ethereal solution was dried over magnesium sulfate, filtered, and evaporated. The residual oil was dissolved in chloroform and acidified with ethereal hydrogen chloride. Evaporation of the solvents gave crude hydrochloride which was recrystallized from ethanol-ether, yields 55-65%.

VIt, ir (nujol): 2640 cm^{-1}; uv (methanol): 218, 264 and 290 nm (ϵ, 24,900, 10,400, and 7,110, respectively); pmr (DMSO-d_6): 1.85 (s, 3H, CH_3), 2.78 (s, 6H, CH_3-N), 3.53 (broad singlet, 2H, CH_2-N), 6.35 (m, 2H, 2-H and 3-H), 7.15 and 7.68 (multiplets, 3H + 2H, aromatic protons and 1-H), 10.8 (broad, 1H, NH^+).

VIu, ir (nujol): 2610 cm^{-1}; uv (methanol): 228. 266, and 303 nm (ϵ, 29,600, 8.950, and 7.070 respectively); pmr (DMSO-d_6): 1.87 (s, 3H, CH_3), 2.73 (broad singlet, 6H, CH_3-N), 3.48 (m, 2H, CH_2-N). 6.35 (m, 2H, 2-H and 3-H), three separate multiplets at 7.20, 7.75, and 7.94 (2H + 1H + 1H, aromatic protons and 1-H).

VIv, ir (nujol): 2600 cm^{-1}; uv (methanol): 218, 265, and 291 nm (ϵ, 24,200, 10,300, and 7,300, respectively): pmr spectrum of the corresponding base in deuteriochloroform: 1.61 (s, 3H CH_3), 2.18 (broad singlet, 6H, CH_3-N), 2.25 (m, 4H, CH_2), 5.98 (m. 1H, 3-H), 6.30 (t, J = 3.5 Hz, 1H, 2-H), 6.9-7.5 (m. 5H, aromatic protons and 1-H).

VIw, ir (nujol): 2320 cm^{-1}; pmr (DMSO-d_6): 1.58 (s, 3H, CH_3), 2.74 (s, 3H, CH_3-N), 6.27 (m, 2H, 2-H and 3-H), two multiplets at 7.12 and 7.65 (3H + 2H, aromatic protons and 1-H).

1-Chloro-4-aminomethyl-*N,N*-4-trimethyl-4*H*-pyrrolo[2,1-*c*][1,4]-benzoxazine Hydrochloride (VIIa).

A solution of sulfuryl chloride (2.2 g.) in 100 ml. of chloroform was added to a solution of VIt (4.5 g.) in 200 ml. of the same solvent at 0°. The reaction mixture was stirred at ambient temperature for 2 hours, evaporated to dryness, and the product was recrystallized from methylenechloride-ether, m.p. 212-214°, yield 4.65 g. (92%); ir (chloroform): 2470 cm^{-1}; uv (methanol): 257, 283, and 288 nm (ϵ, 10,960, 5,480. and 5,170, respectively); pmr (DMSO-d_6): 1.79 (s, 3H, CH_3), 2.86 (s, 6H, CH_3-N), 3.70 (broad singlet, 2H, CH_2-N), 6.46 (s, 2H, 2-H and 3-H), 7.3 (m, 3H, aromatic protons), 8.25 (m, 1H, H-9); pmr (deuteriochloroform): 6.28 (s, 2H, 2-H and 3-H), 7.20 (m, 3H, aromatic protons), 8.25 (m, 1H, H-9), 12.0 (broad, 1H, NH^+).

Methyl 1-Chloro-8-nitro-4*H*-4-methylpyrrolo[2,1-*c*][1,4]benzoxazine-4-acetate (VIIb).

A solution of sulfuryl chloride (0.54 g.) in 20 ml. of dry ether was added to a solution of VIi (1.2 g.) in 60 ml. of the same solvent at 0°. The reaction mixture was stirred at ambient temperature for 24 hours, washed quickly with cold water and 5% sodium bicarbonate, dried over magnesium sulfate, filtered, and evaporated. The crude product was filtered through silica gel using chloroform as eluent. There was obtained 0.7 g. (53%) of crystalline material, m.p. 124-125° (ether-hexane); ir (chloroform): 1735, 1525, and 1500 cm^{-1}; pmr (deuteriochloroform): 1.88 (s, 3H, CH_3), 2.82 (broad singlet, 2H, CH_2), 3.67 (s, 3H, CH_3-O), 6.09 and 6.30 (two doublets, J = 4 Hz, 2H, 2-H and 3-H), 7.17 (d, J_o = 9 Hz, 1H, H-6), two doublets centered at 8.08 (J_o = 9 Hz, J_m = 3 Hz, 1H, H-7), 9.00 (d, J_m = 3 Hz, 1H, H-9).

1-Nitro-4-aminomethyl-*N,N*-4-trimethyl-4*H*-pyrrolo[2,1-*c*][1,4]-benzoxazine Hydrochloride (VIIc).

A cold mixture of 90% nitric acid (8.3 g.) and acetic acid anhydride (50 ml.) was added dropwise to a solution of VIt (3 g.) in acetic anhydride (50 ml.) at -50°. The reaction mixture was stirred at -50° for 1 hour, allowed to come to room temperature, poured into ice-water, neutralized with solid sodium carbonate, and extracted with ether. The combined extracts were washed with water, dried over magnesium sulfate, filtered, and evaporated. A dark oily residue (2.5 g.) was dissolved in chloroform, acidified with ethereal hydrogen chloride, and the solvents were removed *in vacuo*. Recrystallization of the solids from ethanol-ether afforded 1.6 g. (46%) of the title compound, m.p. 247-248°; ir (nujol): 2640, 1520, and 1490 cm^{-1}; uv (methanol): 325 nm (ϵ, 10,550); pmr (DMSO-d_6): 1.8 (s, 3H, CH_3), 2.9 (s, 6H, CH_3-N), 3.9 (broad singlet, 2H, CH_2-N), 7.25 (m, 4H, H-3, 6, 7, 8), 8.1 (m. 1H, H-9), 8.9 (narrow doublet, 1H, 2-H), 11.1 (broad, 1H NH^+); mass spectrum m/e (relative intensity): 287 (1, M^+), 229(5), 199(3), 183(10), 154(5), 58(100).

1-Trifluoroacetyl-*N,N*-4-trimethyl-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-4-acetamide (VIId).

A mixture of VIq (1 g.), trifluoroacetic anhydride (0.84 g.), and benzene (100 ml.) was stirred at 20° for 3 hours, and then heated to reflux for 30 minutes. The cooled solution was washed with water and 10% sodium bicarbonate. Evaporation of the organic phase afforded after chromatography on silica (chloroform) 0.81 g. (60%) of the title compound, m.p. 81-83° (benzene-hexane); ir (chloroform): 1680, 1640, and 1495 cm^{-1}; pmr (deuteriochloroform): 6.25 (d, J = 4.5 Hz, 2H, 2-H and 3-H), 6.8-7.8 (m 4H, aromatic protons).

1-Trifluoroacetyl-4-aminomethyl-*N,N*-4-trimethyl-4*H*-pyrrolo-[2,1-*c*][1,4]benzoxazine Hydrochloride (VIIe).

Compound VIt (250 mg.) was refluxed in trifluoroacetic anhydride (2 ml.) for 2 hours, and the resulting solution was evaporated under reduced pressure. The residue was recrystallized from methylene-chloride-ether to give 150 mg. of white needles, m.p. 122-124°; ir (nujol): 3450, 2700, and 1680 cm^{-1}; pmr (deuteriochloroform): 6.7 (d, J = 4.5 Hz, 2H, 2-H and 3-H).

Mannich Reaction.

Acetic acid (19.8 ml.), 40% aqueous dimethylamine (18 ml.), and 37% formaldehyde (9 ml.) were mixed upon cooling (10-15°) and then added at once to a solution of VIa (10 g.) in ethanol (30 ml.). The reaction mixture was stirred at room temperature for 18 hours, concentrated *in vacuo*, and the resultant suspension was extracted with chloroform. Usual work-up of the organic layer afforded 6 g. of a basic product which was converted into the hydrochloride salt in a standard manner. There was obtained 5.6 g. (40%) of VIIf, m.p. 188-189° (ethanol-ether); ir (chloroform): 2400, 1585, 1550, and 1490 cm^{-1}; uv (methanol): 264 and 291 nm (ϵ, 11,200 and 6,910, respectively); pmr (deuteriochloroform): 1.56 (s, 6H, CH_3), 2.67 (d, J = 4.5 Hz, 6H, CH_3-N), 4.70 (d, J = 4.5 Hz, 2H, CH_2-N), 6.08 and 6.84 (two doublets, J = 4 Hz, 1H + 1H, 2-H and 3-H), 6.9-7.7 (m, 4H, aromatic protons), 12.4 (broad, 1H, NH^+).

Using the same procedure but replacing dimethylamine with morpholine, VIa was converted into VII g. (42%); pmr of the corresponding base in deuteriochloroform: 1.58 (s, 6H, CH_3), 2.56 (m, 4H, CH_2-N in the morpholine ring), 3.50 (s, 2H, CH_2-N), 3.75 (m, 4H, CH_2-O), 5.87 and 6.14 (two doublets, J = 3.5 Hz, 2H, 2-H and 3-H), 7.00 (m, 3H, aromatic protons), 8.17 (m, 1H, H-9). The maleate of this base was crystallized from ethanol, m.p. 149-150°.

1,1'-Isopropylidene-bis-4,4-dimethyl-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazines (VIIIa, R = CH_3, X = H) and (VIIIb, R = CH_3, X = Cl).

A mixture of IVa (8.9 g.), *p*-toluenesulfonic acid (0.9 g.), benzene (500 ml.) and acetone (80 ml.) was refluxed under the Dean-Stark trap for 2 hours. After being washed with 10% sodium bicarbonate, the reaction mixture was evaporated, and the residue was chromatographed on silica gel. Elution with benzene yielded 1.1 g. of VIa, and elution with chloroform gave 10 g. (81%) of VIIIa, m.p. 141-143° (ether-hexane); ir (chloroform): 1600, 1515, and 1500 cm^{-1}; uv (methanol): 268 and 298 nm (ϵ, 23,150 and 22,350, respectively); pmr (deuteriochloroform): singlets at 1.60 and 1.62 (18H, CH_3), two doublets at 5.95 and 6.85 (J = 1.5 Hz, 2H + 2H, pyrrolic protons) 6.95-7.45 (m, 8H, aromatic protons); mass spectrum (relative intensity): 438(59), 423(100), *408.5 (metastable for 438 → 423, 393(11), 204(40), 196(20).

Anal. Calcd. for $C_{29}H_{30}N_2O_2$: C, 79.42; H, 6.90; N, 6.39. Found: C, 78.98; H, 6.88; N, 6.29.

In a similar way, IVb was converted into VIIIb (85%), m.p. 170-173° (ether-hexane); ir (chloroform): 1610, 1595, 1515, and 1495 cm^{-1}; uv (methanol): 270 and 310 nm (ϵ, 21,050 and 22,800, respectively).

Anal. Calcd. for $C_{29}H_{28}Cl_2N_2O_2$: C, 68.63; H, 5.57; N, 5.52. Found: C, 68.50; H, 5.56; N, 5.24.

4-Carboxy-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-4-acetic Acid (XI).

A mixture of IVa (3.18 g.), dimethyl acetylenedicarboxylate (2.84 g.), 1,4-diazabicyclo[2.2.2]octane (0.32 g.) and dry ether (120 ml.) was heated to reflux for 2 hours and evaporated. The oily residue was dissolved in chloroform, and washed with 5% sodium hydroxide and water. Chloroform was removed with rotavapor, and the crude product filtered through a column of silica gel using chloroform as eluent. The major fraction (5 g., 86%), was homogeneous on tlc, and identified by means of spectroscopy as X; ir (chloroform): 1750, 1720, 1640, 1605, and 1510 cm^{-1}; pmr (deuteriochloroform): two singlets at 3.69 and 3.90 (3H + 3H, CH_3-O), 5.25 (s, 1H, =CH-), 6.43 (t, J = 2 Hz, β protons of pyrrole), 7.10 (t, J = 2 Hz, α protons of pyrrole), 7.45 (m, 4H, aromatic protons).

This dimethyl ester X (0.6 g.) was dissolved in 50 ml. of methanol, 4 ml. of 10% sodium hydroxide was added, and the reaction mixture was refluxed for 2 hours. Methanol was removed *in vacuo*, the remaining paste was diluted with water and acidified with hydrochloric acid. The product was extracted with chloroform, and crystallized from chloroform-hexane. There was obtained 0.4 g. (74%) of XI, m.p. 125-126°; ir (nujol): 1725, 1705, 1595, and 1500 cm^{-1}; uv (methanol): 264 and 293 nm (8,560 and 6,570, respectively); pmr (DMSO-d_6): two doublets at 3.00 and 3.38 (J_{gem} = 16 Hz, 2H, CH_2-CO), 6.24 (m, 2H, 2-H and 3-H), 7.0-7.6 (m, 5H, aromatic protons and 1-H). Stability of this dicarboxylic acid appears to be limited.

Anal. Calcd. for $C_{14}H_{11}NO_5$: N, 5.13. Found: N, 4.99.

Dimethyl 3-(2-Hydroxyanilino)phthalate (XIII).

A solution of IVa (3.18 g.) and dimethyl acetylenedicarboxylate (2.84 g.) in dioxan (120 ml.) was refluxed for 48 hours. The solvent was removed *in vacuo*, and the residue was triturated with ethyl acetate. The crystalline material was collected by filtration, and recrystallized from methanol, m.p. 195-196°, yield 2.5 g.; ir (nujol): 3385, 3000 (broad), 1745, 1690, 1630, and 1600 cm^{-1}; uv (acetonitrile): 242 and 287 nm (ϵ = 7,050 and 8,830, respectively); pmr (DMSO-d_6): 3.9 (s, 6H, CH_3O), 6.7-7.5 (m, 7H, aromatic protons), 7.9 (broad, 1H).

Anal. Calcd. for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 64.00; H, 5.13; N, 4.67.

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