Synthesis of Novel Imidazo[1,2-*a*][3,1]benzothiazines **4**, Imidazo[1,2-*a*]-[1,2,4]benzotriazines **5**, and 4*H*-Imidazo[2,3-*c*]pyrido[2,3-*e*][1,4]oxazines **6**

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Starting from the readily available 2-aminobenzhydrols (**7**), 3-amino-1,2,4-benzotriazine (**11**) and 2-amino-3-pyridinol (**12**), novel derivatives of 5-phenyl-5*H*-imidazo[1,2-*a*][3,1]benzothiazine-2-carboxylic acid, ethyl ester (**4**), imidazo[2,1-*c*][1,2,4]benzotriazine-2-carboxylic acid, ethyl ester (**5**) and 4*H*-imidazo[2,3-*c*]pyrido-[2,3-*e*][1,4]oxazine (**6**) were prepared.

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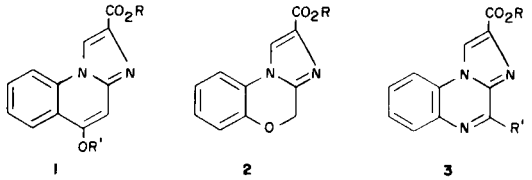
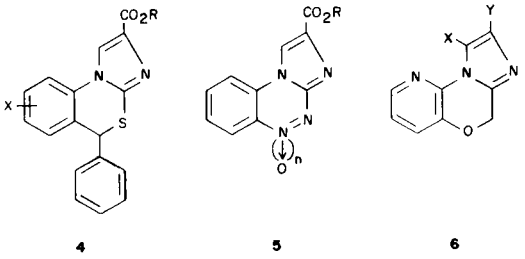
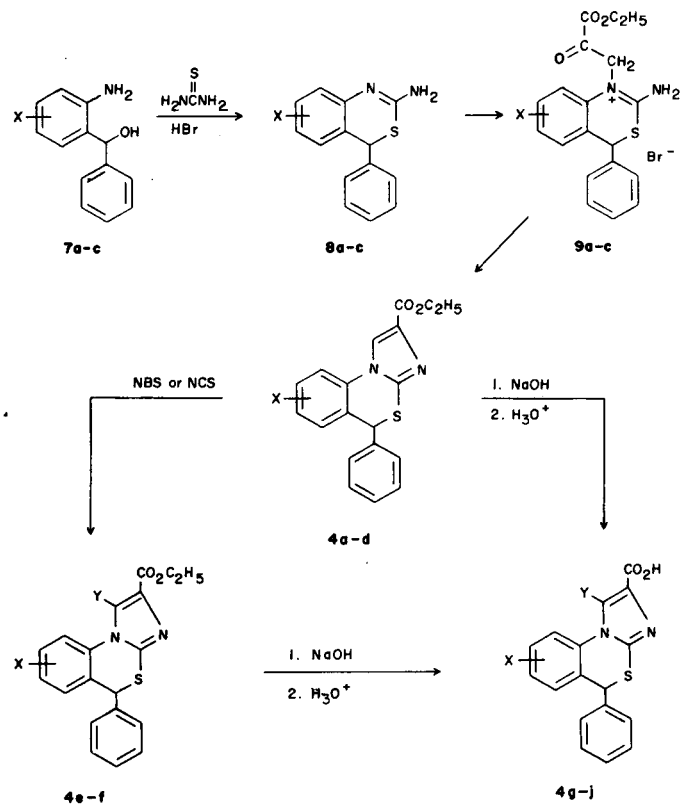
In search for new drug candidates in the antiallergy field, we have devised syntheses of new skeletal variants of biologically active imidazoquinolines **1**, imidazobenzoxazines **2** and imidazoquinoxalines **3** [2-4].



In this paper we wish to report the synthesis of novel imidazo[1,2-*a*][3,1]benzothiazines **4**, imidazo[1,2-*a*][1,2,4]-benzotriazines **5** and imidazo[2,3-*c*]pyrido[2,3-*e*][1,4]oxazines **6**.



Scheme I

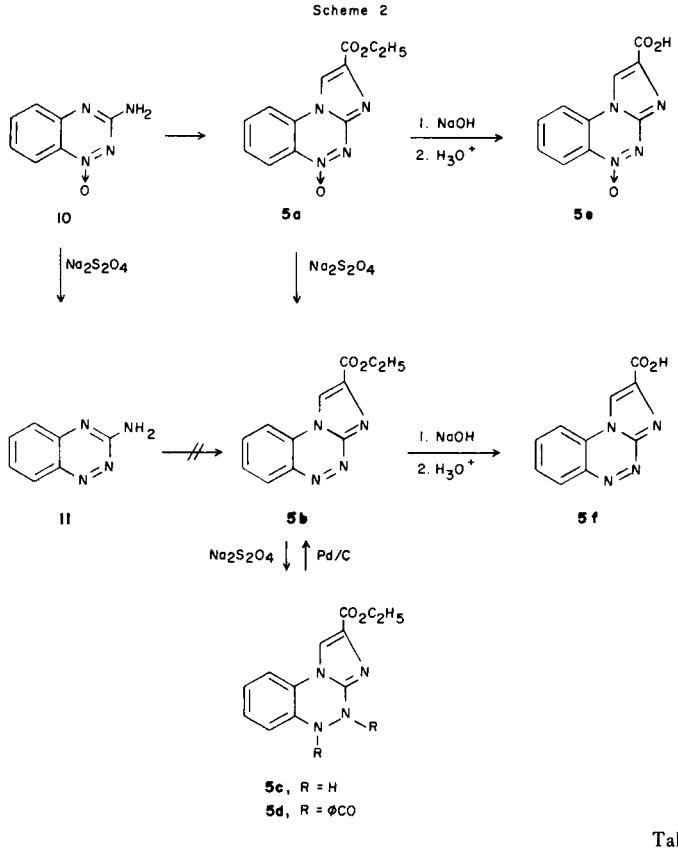


We have prepared amidines **8a-c** following a published procedure [5] using benzhydrols. Compound **7a-c** condensed with thiourea in concentrated hydrobromic acid under reflux conditions. Benzothiazolinium bromides **9a-c** have been obtained from 2-amino-4-phenyl-4*H*-3,1-benzothiazines **8a-c** and ethyl bromopyruvate in dimethoxyethane at room temperature for 24 hours. A final conversion of the bromide salts **9a-c** to the corresponding imidazoles **4a-d** was effected in ethanol at reflux (Scheme 1).

Bromination of the imidazole ring of **4a** was effected with *N*-bromosuccinimide in chloroform at reflux to produce bromoimidazole **4e** in good yield. The chloroimidazole **4f** was obtained in very good yield under similar conditions using *N*-chlorosuccinimide. The carboxylic acids **4g-j** were prepared by saponification of the corresponding imidazole esters **4a-d**. Condensation of 3-amino-1,2,4-benzotriazine 1-oxide (**10**) [6] with ethyl bromopyruvate in tetrahydrofuran at reflux in the presence of ethanol furnished the imidazole **5a** in good yield. 3-Amino-1,2,4-benzotriazine (**11**) was obtained in high yield by treatment of oxide **10** with sodium dithionite in aqueous ethanol. Attempts to prepare imidazole **5b** in analogous manner as **5a**, using 3-amino-1,2,4-benzotriazine (**11**) failed. However, oxide **5a** was converted to imidazoles **5b-c** in mixture using sodium dithionite in aqueous DMF in the presence of sodium bicarbonate (Scheme 2).

The identity of imidazole **5c** was deduced by mass spectrometry analysis of the mixture and by formation of a dibenzoyl derivative **5d** upon treatment with benzoyl chloride. Transformation of imidazole **5c** into imidazole **5b** was

Scheme 2



performed by subjecting the mixture under dehydrogenation conditions with palladium on charcoal in xylene (Scheme 2, Tables I-II).

We have prepared 3-amino-2*H*-pyrido[3,2-*b*][1,4]oxazine (**14**) in two steps from commercially available 2-amino-3-pyridinol (**12**). The aminonitrile **13** was prepared by treatment of aminopyridinol **12** with chloroacetonitrile in acetone with anhydrous potassium carbonate. The amidine **14** was obtained through a cyclization of nitrile **13** in methanol using sodium methoxide. The imidazoles **6a-c** were prepared using one of the following methods. In one case amidine **14** was converted into the corrresponding acetal **15** in excellent yield with aminoacetaldehyde dimethylacetal. In order to achieve the formation of imidazole **6a** we have found that titanium tetrachloride in boiling toluene affords the highest yields. Treatment of ketal **15** with dilute mineral acid only results in the formation of lactam **16** [7]. In a more direct manner, we have prepared amidines **6b-c** by condensation of the appropriate α-aminonitriles **17a-b** with amidine **14** in ethanol (Scheme 3).

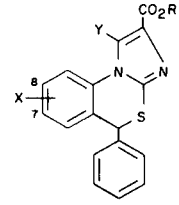
EXPERIMENTAL

General.

All experiments, with the exception of those in which water is used as solvent, were carried out under nitrogen. The following solvents were dis-

Table I

5-Phenyl-5*H*-imidazo[1,2-*a*][3,1]benzothiazine-2-carboxylic Acids and Ethyl Esters

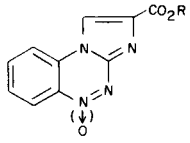


Compound No.	X	Y	R	Mp °C	Recrystallization Solvent	Yield %	Formula	Analyses % Calcd./Found C	H	N
4a	H	H	C_2H_5	217 [a]	EtOH-Et_2O	96	$C_{19}H_{17}BrN_2O_2S$	54.68	4.11	6.71
							417.33	54.64	4.07	6.77
4b	H	H	C_2H_5	155-156	EtOH-Et_2O	86	$C_{19}H_{16}N_2O_2S$	67.83	4.79	8.33
							336.40	67.51	4.76	8.34
4c	7-Cl	H	C_2H_5	242-243	AcOH-hexane	96	$C_{19}H_{15}ClN_2O_2S$	61.54	4.08	7.56
							370.79	61.30	4.24	7.47
4d	8-Cl	H	C_2H_5	235-236 [a]	*i*-PrOH-hexane	80	$C_{19}H_{16}BrClN_2O_2S$	50.51	3.57	6.20
							451.78	50.36	3.58	6.17
4e	H	Br	C_2H_5	181-182	EtOAc-hexane	57	$C_{19}H_{15}BrN_2O_2S$	54.94	3.67	6.75
							415.31	54.96	3.71	6.70
4f	H	Cl	C_2H_5	175-176	EtOAc-hexane	82	$C_{19}H_{15}ClN_2O_2S$	61.53	4.08	7.56
							370.85	61.87	4.24	7.53
4g	H	H	H	255-256	EtOH-H_2O	71	$C_{17}H_{12}N_2O_2S$	66.22	3.92	9.09
							308.36	65.82	4.19	8.98
4h	H	Br	H	201-202	CH_2Cl_2-hexane	71	$C_{17}H_{11}BrN_2O_2S$	52.72	2.86	7.24
							387.26	52.66	3.04	7.07
4i	7-Cl	H	H	296-297	DMSO-H_2O	57	$C_{17}H_{11}ClN_2O_2S$	59.56	3.21	7.55
							342.80	59.72	3.44	7.79
4j	8-Cl	H	H	220-221	EtOH-H_2O	70	$C_{17}H_{11}ClN_2O_2S$	59.56	3.21	7.55
							342.80	59.24	3.44	7.77

[a] Hydrobromide salt.

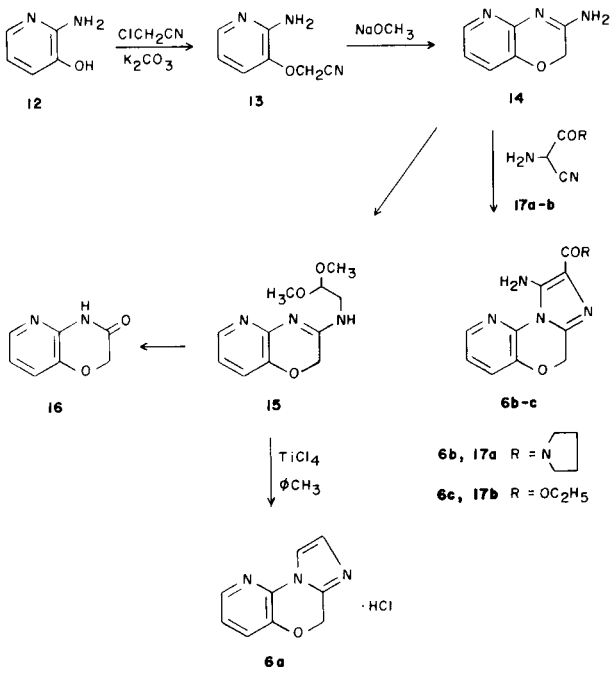
Table II

Imidazo[1,2-*a*][1,2,4]benzotriazine-2-carboxylic Acids and Ethyl Esters



Compound No.	n	R	Mp °C	Recrystallization Solvent	Yield %	Formula	Analyses % Calcd./Found C	H	N
5a	1	C_2H_5	267-268	CH_3CN-Et_2O	59	$C_{12}H_{10}N_4O_3$	55.81	3.90	21.70
						258.23	55.45	3.90	21.70
5b	0	C_2H_5	239-240	CH_2Cl_2-hexane	25	$C_{12}H_{10}N_4O_2$	59.50	4.16	23.13
						242.23	59.12	4.18	23.29
5e	1	H	279-280	DMF-Et_2O	82	$C_{10}H_6N_4O_3$	52.18	2.63	24.34
						230.18	51.97	2.70	24.40
5f	0	H	264-265 [a]	DMF-Et_2O	85	$C_{10}H_6N_4O_2$·DMF	54.35	4.56	24.38
						287.27	53.96	4.56	24.27

Scheme 3



tilled prior to use: 1,2-dimethoxyethane and tetrahydrofuran (from sodium metal), toluene was stored over sieves (Linde 4A). Commercial starting compounds were used without further purification. Elemental microanalyses were carried in the Analytical Department of this laboratory. The ir spectra were done on a Perkin-Elmer diffraction grating instrument and the uv spectra were recorded on a Unicam spectrophotometer. The melting points were taken on a Thomas-Hoover apparatus and are uncorrected. The nmr spectra were recorded on a Varian CFT 20 apparatus and mass spectra on a Hitachi RMU-60 spectrometer. Organic extracts were dried over anhydrous magnesium sulfate and solvents were always removed under vacuum. Merck silica gel 60(70-230) was used for column chromatography (tlc) was carried out on silica gel plates using methanol-chloroform combinations in varying proportions. The chromatograms were developed in an iodine chamber.

2-Amino-4-phenyl-4*H*-3,1-benzothiazine Derivatives (**8a-c**).

General Procedure.

2-Aminobenzhydrol (**7a**) (13.30 g, 66.8 mmoles) and thiourea (5.10 g, 67.0 mmoles) were stirred in 48% hydrobromic acid (33 ml) and heated at reflux for 90 minutes. The brownish gum which deposited was separated, dissolved in chloroform and treated with ammonium hydroxide to generate the free base. The organic phase was washed with water, brine and dried. Evaporation afforded a crystalline residue which crystallized from chloroform-hexane and the amidine **8a** (12.72 g, 80%) mp 143-144° (lit [5] mp 148-149°).

2-Amino-6-chloro-4-phenyl-4*H*-3,1-benzothiazine (**8b**).

Compound **8b** was prepared in the same manner and obtained in 79% yield, mp 169-170° (lit [5] mp 170-171°); ir (nujol): ν max 3440, 3280, 1640, 1570 cm^{-1}; nmr (deuteriochloroform): δ 4.75 (broad, 2H, NH_2), 5.15 (s, 1H, CH), 7.2 (m, 8H, ArH).

Anal. Calcd. for $C_{14}H_{11}ClN_2S$: C, 61.19; H, 4.04; N, 10.20. Found: C, 61.16; H, 4.11; N, 10.12.

2-Amino-4-chlorobenzhydrol (**7c**).

2-Amino-4-chlorobenzophenone (90.00 g, 388 mmoles) was stirred in ethanol (800 ml) at reflux and sodium borohydride (13.14 g, 347 mmoles) was added to the mixture in small portions. After 2 hours, the mixture was cooled and excess borohydride was destroyed under nitrogen by addition of some acetic acid. A part of the solvent was stripped, the mixture was then poured in water (1 liter) and extracted with methylene chloride. The combined extracts were washed with water, brine, dried and concentrated. The title compound (74.01 g, 82%) afforded white crystals from methylene chloride-hexane, mp 99-100°; ir (nujol): ν max 3360, 3220, 1605, 1585, 1490 cm^{-1}; nmr (deuteriochloroform): δ 3.35 (broad, 3H, NH_2 and OH), 5.75 (s, 1H, CH), 7.00 (m, 3H, ArH), 7.25 (s, 5H, ArH).

Anal. Calcd. for $C_{13}H_{12}ClNO$: C, 66.81; H, 5.18; N, 5.99. Found: C, 66.77; H, 5.16; N, 5.94.

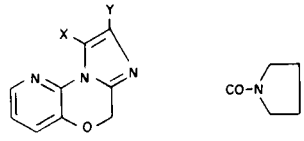
2-Amino-7-chloro-4-phenyl-3,1-benzothiazine (**8c**).

This compound was obtained in 80% from 2-amino-4-chlorobenzhydrol (**7c**), mp 165-166°; ir (nujol): ν max 3460, 3370, 3280, 3040, 1640, 1575, 1560 cm^{-1}; nmr (DMSO-d_6): δ 5.45 (s, 1H, CH), 7.1 (m, 8H, ArH).

Anal. Calcd. for $C_{14}H_{11}ClN_2S$: C, 61.19; H, 4.04; N, 10.20. Found: C, 60.90; H, 4.06; N, 10.05.

Table III

Imidazo[2,3-*c*]pyrido[2,3-*e*][1,4]oxazines



Compound No.	X	Y	Mp °C	Recrystallization Solvent	Yield %	Formula	Analyses % Calcd./Found C	H	N
6a	H	H	295-297 [b]	AcOH-hexane	70	$C_9H_7N_3O$	51.56 51.63	3.85 3.67	20.04 20.08
6b	NH_2		207-208	AcOH-hexane	23	$C_{14}H_{15}N_5O_2$ 285.30	58.93 58.95	5.30 5.32	24.55 24.72
6c	NH_2	$CO_2C_2H_5$	155	*i*-PrOH	10	$C_{12}H_{12}N_4O_3$ 260.25	55.38 55.30	4.65 4.73	21.53 21.85

[a] Crystallized with 1 mole DMF. [b] Hydrochloride salt.

5*H*-Imidazole[1,2-*a*][3,1]benzothiazine-2-carboxylic Acid, Ethyl Esters (**4a-d**, Table 1).

General Procedure.

A mixture of **8a** (10.00 g, 41.6 mmoles) and ethyl bromopyruvate (5.25 ml, 41.8 mmoles) in 1,2-dimethoxyethane (200 ml) was stirred overnight at room temperature. The beige precipitate was collected by filtration, washed with diethyl ether and air-dried to afford 5.44 g (37%) of **9a**, mp 208-209° as a powder not purified at this point; nmr (DMSO-d_6): δ 1.13 (t, J = 7 Hz, 3H, CH_3), 5.67 (s, 1H, CH).

A suspension of the above crude **9a** (1.00 g, 2.29 mmoles) was subjected directly to the cyclization procedure in ethanol (15 ml) at reflux for 90 minutes. The solution was concentrated, the residue triturated in diethyl ether and recrystallized from ethanol-diethyl ether giving a beige powder 810 mg (96%) of **4a** of mp 217°; uv: λ max 251 nm (ε 17600); nmr (DMSO-d_6): δ 1.30 (t, J = 7 Hz, 3H, CH_3), 4.20 (q, J = 7 Hz, 2H, CH_2), 5.90 (s, 1H, CHS), 7.19 (m, 9H, ArH), 8.81 (s, 1H, C=CHN). The corresponding free base **4b** was generated in chloroform with 10% aqueous potassium carbonate. Evaporation of the dried extracts gave a tan residue which recrystallized from ethanol-water as white crystals (86%) of mp 155-156°; ir (nujol): ν max 1695 cm^{-1}; nmr (DMSO-d_6): δ 1.30 (t, J = 7 Hz, 3H, CH_3), 4.25 (q, J = 7 Hz, 2H, CH_2), 5.85 (s, 1H, CHS), 7.30 (m, 9H, ArH), 8.75 (s, 1H, C=CHN).

1-Bromo-4-phenyl-5*H*-imidazo[1,2-*a*][3,1]benzothiazine-2-carboxylic Acid, Ethyl Ester (**4e**, Table I).

A mixture of **4b** (1.70 g, 5.05 mmoles), *N*-bromosuccinimide (0.90 g, 5.01 mmoles), 50 ml of chloroform was refluxed for 24 hours. The succinimide which precipitated by addition of hexane was collected by filtration; the filtrate was concentrated and residue triturated in diethyl ether to yield **4e** as a brownish solid 1.20 g (57%) mp 180-181°. Recrystallization of a small amount gave tan crystals mp 181-182°; ir (nujol): ν max 1710 cm^{-1}; uv (methanol): λ max 233 nm (ε 20390); nmr (deuteriochloroform): δ 1.35 (t, J = 7 Hz, 3H, CH_3), 4.35 (q, J = 7 Hz, 2H, CH_2), 5.25 (s, 1H, CHS), 7.20 (m, 5H, ArH), 7.0-7.7 (m, 3H, ArH).

1-Chloro-4-phenyl-5*H*-imidazo[1,2-*a*][3,1]benzothiazine-2-carboxylic Acid, Ethyl Ester (**4f**, Table I).

A mixture of **4b** (6.20 g, 18.43 mmoles), *N*-chlorosuccinimide (2.50 g, 18.72 mmoles), 100 ml of chloroform was refluxed for 4 hours. The mixture was saturated with hexane to remove succinimide by filtration. The filtrate was concentrated and residual solid was triturated in diethyl ether-hexane at 0°. Recrystallization of the bulk of material from ethyl acetate-hexane gave 5.41 g (82%) of **4f** of mp 175-176°; ir (nujol): ν max 1700 cm^{-1}; nmr (deuteriochloroform): δ 1.39 (t, J = 7 Hz, 3H, CH_3), 4.35 (q, J = 7 Hz, 2H, CH_2), 5.35 (s, 1H, CHS), 7.20 (m, 8H, ArH), 8.00 (m, 1H, ArH).

5*H*-Imidazo[1,2-*a*][3,1]benzothiazine-2-carboxylic Acids **4g-j** (Table I).

General Procedure.

A mixture of 1-bromo-5-phenyl-5*H*-imidazo[1,2-*a*][3,1]benzothiazine-2-carboxylic acid, ethyl ester (**4e**) (4.63 g, 9.00 mmoles), 2 *M* aqueous sodium hydroxide (80 ml) and ethanol (80 ml) was stirred at 70° for 30 minutes. Cautious acidification with hydrochloric acid resulted in precipitation of the title acid as a white powder. Filtration and recrystallization from methylene chloride-hexane afforded a crop of white crystals (3.06 g, 71%) of **4h** of mp 201-202°; ir (nujol): ν max 3000, 1700 cm^{-1}; nmr (DMSO-d_6): δ 5.90 (s, 1H, CHS), 7.49 (m, 9H, ArH).

3-Amino-1,2,4-benzotriazine 1-Oxide (**10**).

Cyanamide (93.0 g, 2.21 moles) dissolved in concentrated hydrochloric acid (150 ml) was cooled and added dropwise to a solution of 2-nitroaniline (50.00 g, 362 mmoles) in glacial acetic acid (150 ml) under reflux conditions. After, the mixture was heated for 30 minutes, cooled and basified with 2 *N* sodium hydroxide. The mixture was then refluxed during 10 minutes and allowed to cool to deposit a yellow precipitate. The powder was filtered, washed with ether and dried. Recrystallization from glacial acetic acid-hexane afforded 55.77 g (95%) of **10** of mp 278-279° (lit [8] mp 267-268°).

Anal. Calcd. for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.55. Found: C, 51.69; H, 3.72; N, 34.64.

3-Amino-1,2,4-benzotriazine (**11**).

A suspension of 3-amino-1,2,4-benzotriazine 1-oxide **10** (10.00 g, 61.7 mmoles) was stirred in 35% aqueous ethanol (55 ml) with sodium dithionite (20.00 g, 114.9 mmoles) under reflux conditions for 1 hour. Most of the ethanol was stripped, the cooled mixture was treated with 10% aqueous sodium hydroxide and extracted with several portions of chloroform. The combined extract was washed with water, brine, dried and concentrated to yield 7.97 g (88%) of **11** as yellow crystals of mp 205-206° (lit [8] mp 208-210°) obtained by recrystallization from ethyl acetate-hexane; ir (nujol): ν max 3270, 3130, 1665, 1605, 1550 cm^{-1}; nmr (deuteriochloroform): δ 5.65 (broad, 2H, NH_2), 7.59 (m, 4H, ArH).

Anal. Calcd. for $C_7H_6N_4$: C. 57.52; H, 4.14; N, 38.34. Found: C, 57.32; H, 3.88; N, 38.70.

Imidazo[1,2-*a*][1,2,4]benzotriazine-2-carboxylic Acid Ethyl Ester 5-Oxide (**5a**, Table II).

A suspension of 3-amino-1,2,4-benzotriazine 1-oxide (5.60 g, 34.6 mmoles) was stirred in dry tetrahydrofuran (300 ml) with ethyl bromopyruvate (6 ml) at room temperature for 2 hours and at reflux for 24 hours. Ethanol (1.5 liters) was added and the mixture was refluxed for 12 hours. The yellow powder which deposited upon cooling, was filtered, washed with ethanol and air-dried. Recrystallization of this material from acetonitrile-diethylether gave 5.25 g (59%) of **5a** of mp 267-268°; ir (nujol): ν max 1700, 1265 cm^{-1}; nmr (DMSO-d_6): δ 1.37 (t, J = 7 Hz, 3H, CH_3), 4.42 (q, J = 7 Hz, 2H, CH_2), 7.82, 8.17, 8.60 (m, 4H, ArH), 9.37 (s, 1H, ArH).

Imidazo[1,2-*a*][1,2,4]benzotriazine-2-carboxylic Acid Ethyl Ester (**5b**, Table II).

Sodium dithionite (20.00 g, 115.9 mmoles) was added in portions to a suspension of imidazo[1,2-*a*][1,2,4]benzotriazine-2-carboxylic acid ethyl ester 5-oxide (**5**) (10.00 g, 38.7 mmoles) stirred in aqueous DMF (66%, 300 ml) under reflux in the presence of sodium bicarbonate (200 ml, saturated aqueous solution). After 1 hour, more sodium dithionite (20.00 g, 114.9 mmoles) was added in the same manner for 3 hours. The white powder obtained upon cooling of the mixture was filtered and dried. This material showed 2 new spots on silica gel plates using a 1:10 methanol-chloroform solvent combination. The crude powder was stirred 90 minutes in xylene (80 ml) at reflux in the presence of palladium on charcoal (10%, 1.00 g). The catalyst was removed by filtration and concentration of the filtrate gave 2.32 g (25%) of **5b** of mp 239-240° obtained as white crystals from methylene chloride-hexane; ir (nujol): ν max 1700, 1601, 1579, 1260 cm^{-1}; uv (methanol): λ max 342 nm (ϵ 12000), 238 (ϵ 31000); nmr (DMSO-d_6): δ 1.39 (t, J = 7 Hz, 3H, CH_3), 4.40 (q, J = 7 Hz, 2H, CH_2OCO), 7.95 (m, 2H, ArH), 8.60 (d, J = 8 Hz, 2H, ArH), 9.46 (s, 1H, C=CHN).

4,5-Dibenzoyl-4,5-dihydroimidazo[2,1-*a*][1,2,4]benzotriazine-2-carboxylic Acid, Ethyl Ester (**5d**).

Benzoyl chloride (10 ml) was added dropwise to a crude mixture of **5b** and **5c** (4.50 g) stirred in methylene chloride (150 ml) and aqueous sodium hydroxide (2.5 *N*, 10 ml) cooled between 0-5°. After 15 minutes, the organic phase was separated, washed with water, brine and dried. The solution was concentrated to afford a residue which crystallized from methylene chloride-hexane as white crystals (1.80 g, 22%) of **5d** of mp 188-189°; ir (nujol): ν max 1735, 1700, 1675 cm^{-1}; uv (methanol): λ max 226 nm (ϵ 35700); nmr (deuteriochloroform): δ 1.35 (t, J = 7 Hz, 3H, CH_3), 4.30 (q, J = 7 Hz, 2H, CH_2OCO), 7.49 (m, 15H, ArH).

Anal. Calcd. for $C_{26}H_{20}N_4O_4$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.32; H, 4.52; N, 12.09.

Imidazo[2,1-*a*][1,2,4]benzotriazine-2-carboxylic Acid (**5e-f** Table II).

General Procedure.

A mixture of ester **5b** (2.00 g, 8.25 mmoles), 2.5 *M* aqueous sodium hydroxide (60 ml) and ethanol (60 ml) was stirred at reflux for 1 hour. The clear solution was concentrated to half volume, cooled and cautiously acidified to afford the title compound as yellow powder. Recrystallization from DMF-diethylether gave 1.51 g (85%) of **5f** of mp 264-265°; ir (nujol): ν max 1680 cm^{-1}; uv (methanol): λ max 344 nm (ϵ 8560), 234 (ϵ 23250).

2-Amino-3-cyanomethoxypyridine (**13**).

A mixture of 2-amino-3-pyridinol (**12**) (11.00 g, 100 mmoles), anhydrous potassium carbonate (10.0 g) and chloroacetonitrile (19.00 g, 252 mmoles) was stirred in acetonitrile (100 ml) at reflux for 6 hours. The white insoluble material was filtered; the clear filtrate was concentrated and residue filtered through silica gel using chloroform to yield an orange powder (8.35 g). Recrystallization of the bulk of material from ethyl acetate-hexane afforded 7.15 g (48%) of **13** of mp 100-101°; ir (nujol): ν max 3480, 3280, 3120 cm^{-1}; uv (methanol): λ max 297 nm (ϵ 6060), 234 (ϵ 10080); nmr (deuteriochloroform): δ 4.78 (m, 4H, CH_2O and NH_2), 6.5-7.8 (m, 3H, ArH).

Anal. Calcd. for $C_7H_7N_3O$: C, 56.37; H, 4.73; N, 28.18. Found: C, 56.69; H, 4.59; N, 28.17.

3-Amino-2*H*-pyrido[3,2-*b*][1,4]oxazine (**14**).

A solution of 2-amino-3-cyanomethoxypyridine (**13**) (5.00 g, 31.0 mmoles) in methanol (50 ml) was refluxed for 4 hours in the presence of sodium methoxide (2.2 meq). The solution was concentrated and residue triturated in ethyl acetate to yield a yellow powder (3.50 g, 70%) of mp 170-171°. Recrystallization from 2-propanol afforded yellow crystals mp 173-174°; ir (nujol): ν max 3350, 3320, 2900 cm^{-1}; uv (methanol): λ max 308 nm (ϵ 14420), 265 (ϵ 4740); nmr (DMSO-d_6): δ 4.50 (s, 2H, CH_2O), 6.91 (m, 2H, ArH), 7.30 (s, 2H, NH_2), 7.79 (m, 1H, ArH).

Anal. Calcd. for $C_7H_7N_3O$: C, 56.37; H, 4.73; N, 28.18. Found: C, 56.40; H, 4.80; N, 28.33.

N-(2*H*-Pyrido[3,2-*b*][1,4]oxazin-3-yl)aminoacetaldehyde Dimethylacetal (**15**).

A mixture of 3-amino-2*H*-pyrido[3,2-*b*][1,4]oxazine (**14**) (10.00 g, 67.0 mmoles) and aminoacetaldehyde dimethylacetal (7.05 g, 67.1 mmoles) was refluxed in ethanol (100 ml) for 5 hours. The solution was concentrated and residue was chromatographed on a silica gel column with a 1:10 methanol-chloroform solvent combination to give a brown solid. Recrystallization from ethyl acetate yielded 13.08 g (82%) of **15** of mp 136-137°; ir (chloroform): ν max 3430, 3240, 1625, 1585, 1542 cm^{-1}; nmr (deuteriochloroform): δ 3.40 (s, 6H, CH_3O), 3.69 (m, 2H, CH_2), 4.53 (m, 3H, CH_2O and CHO), 5.61 (broad, 1H, NH), 6.91 (m, 2H, ArH) and 7.95 (m, 1H, ArH).

2*H*-Pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one (**16**).

N-(2*H*-Pyrido[3,2-*b*][1,4]oxazin-3-yl)aminoacetaldehyde dimethylacetal (1.00 g, 4.22 mmoles) was refluxed during 30 minutes in hydrochloric acid (8 *N*, 20 ml). The tarry residue was obtained by filtration and the clear filtrate was allowed to cool to yield greyish needles (248 mg, 39%) of **16** of mp 203-204° (lit [7] mp 205-206°); nmr (DMSO-d_6): δ 5.4 (s, 2H, CH_2), and 7.6 (m, 3H, ArH).

4*H*-Imidazo[2,3-*c*]pyrido[2,3-*e*][1,4]oxazine Hydrochloride (**6a**, Table III).

Titanium tetrachloride (6.5 ml, 11.22 g, 59.2 mmoles) was added to a mechanically stirred solution of *N*-(2*H*-pyrido[3,2-*b*][1,4]oxazin-3-yl)aminoacetaldehyde dimethylacetal **15** (6.70 g, 28.3 mmoles) in toluene (500 ml) at reflux. The suspension was stirred under these conditions for 3 hours. The cooled mixture was extracted with water (200 ml), filtered through celite to remove insoluble material and basified with 10% aqueous potassium carbonate. Several extractions with methylene chloride, followed by washing of the extracts with water, brine, drying and stripping of solvent finally yielded 4.10 g (84%) of the free base of **6a**. Ethereal hydrogen chloride was added in excess to a solution of this yellow powder in diethyl ether. The white precipitate was filtered and recrystallized from acetic acid-hexane to afford white crystals of **6a** (4.13 g, 70%) of mp 295-297° dec; ir (nujol): ν max 2520, 1840 and 1820 cm^{-1}; uv (methanol): λ max 293 nm (ϵ 9668); nmr (deuteriochloroform: (free base) δ 5.35 (s, 2H, CH_2), 7.50 (m, 5H, ArH).

2-[1-Pyrrolidinyl)carbonyl]-4*H*-imidazo[2,3-*c*]pyrido[2,3-*e*][1,4]oxazine-1-amine (**6b**, Table III).

A mixture of 3-amino-2*H*-pyrido[3,2-*b*][1,4]oxazine (**14**) (8.50 g, 57 mmoles) and 2-amino-2-cyanoacetylpyrrolidine (11.35 g, 74 mmoles) was refluxed in ethanol (65 ml) for 6 hours. Ice-water was added to the mixture, the precipitate was filtered and recrystallized from glacial acetic acid-hexane to afford 3.75 g (23%) of **6b** of mp 207-208°; ir (nujol): ν max 3420 and 3320 cm^{-1} (NH_2) and 1590 cm^{-1} (CO); uv (methanol): λ max 281 nm (ϵ 19515) and 237 (ϵ 13750); ^{1}H-nmr (DMSO-d_6): δ 1.8 (m, 4H, CH_2), 3.65 (m, 4H, CH_2), 5.2 (s, 2H, CH_2), 6.85 (s, 2H, NH_2), 7.4 and 8.05 (m, 3H, ArH).

1-Amino-4*H*-imidazo[2,3-*c*]pyrido[2,3-*e*][1,4]oxazine-2-carboxylic Acid, Ethyl Ester (**6c**, Table III).

A mixture of 3-amino-2*H*-pyrido[3,2-*b*][1,4]oxazine (**14**) (8.00 g, 53.6 mmoles) and 2-amino-2-cyanoacetic acid, ethyl ester (8.00 g, 62.4 mmoles) was refluxed in ethanol (100 ml) for 9 hours. The mixture was cooled, the precipitate was collected by filtration and recrystallized thrice from isopropanol to yield 1.31 g (10%) of **6c** of mp 155°; ir (nujol): ν max 3460, 3340, 1670 cm^{-1}; uv (methanol): λ max 289 nm (ϵ 15805), 270 (ϵ 8785); nmr (deuteriochloroform): δ 1.40 (t, J = 7 Hz, 3H, CH_3), 4.35 (q, J = 7 Hz, 2H, CH_2), 5.15 (s, 2H, CH_2O), 6.65 (s, 2H, NH_2), 7.25 (m, 2H, ArH) and 8.0 (m, 1H, ArH).

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