Research on Heterocyclic Compounds. XXIII. Phenyl Derivatives of Fused Imidazole Systems

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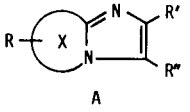
Received March 14, 1989

The reaction of various heteroarylamines with ethyl 2-benzoyl-2-bromoacetate was used to obtain some imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrimidines, imidazo[2,1-*b*]thiazoles and imidazo[2,1-*b*]benzothiazoles characterized by the presence of a phenyl moiety on the imidazole ring. In the case of thiazole and benzothiazole derivatives, unexpected by-products were isolated and their structures elucidated.

J. Heterocyclic Chem., **26**, 1875 (1989).

During our research on heterocyclic compounds acting as antiinflammatory agents, we synthesized many acidic and non-acidic derivatives of some fused imidazole systems with a bridgehead nitrogen atom, such as imidazo-[1,2-*a*]pyridine [1], imidazo[1,2-*a*]pyrimidine [2], imidazo-[1,2-*c*]pyrimidine [3], imidazo[1,2-*a*]pyrazine [4], imidazo-[1,2-*b*]pyridazine [5], imidazo[2,1-*b*]thiazole and imidazo-[2,1-*b*]benzothiazole [6,7].

All these compounds can be represented by the structural model **A** depicted in Figure 1, where X stands for the ring fused with imidazole, R for one or more substituents, and R' (or R'') for an acidic (-COOH, $-CH_2COOH$ *etc.*) or non-acidic ($-CH_3$, CF_3, $-CONH_2$ *etc.*) moiety.

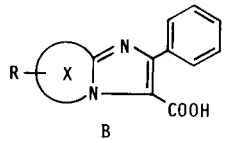


A

Figure 1

As a rule, most of these compounds showed more or less remarkable antiinflammatory and related activities, whose level became comparable to that of indomethacin only at larger doses. These observations might be explained on the basis of the structure of the prostaglandin synthetase receptor site, that is cyclooxygenase active site, proposed by Gund and Shen [8] for indomethacin and other acidic antiinflammatory agents. This site is characterized by a hydrophobic groove in which a suitable moiety of the inhibitor must fit. The absence of such an hydrophobic moiety in our compounds might be the reason of their moderate activity in comparison with indomethacin.

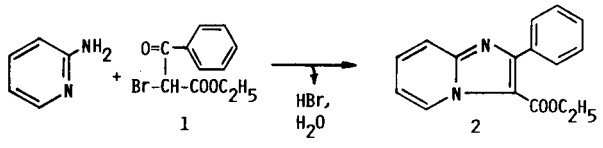
Consequently, we have devised to synthesize some compounds related to the modified structural model **B** depicted in Figure 2, which is characterized by the presence of a phenyl group, in order to verify if these phenyl derivatives are more active than the corresponding compounds of the **A** type. In this case the mechanism of action of such molecules should be indirectly confirmed.



B

Figure 2

The synthetic method chosen to prepare new compounds of the **B** type is closely similar to the general procedure reported in our above mentioned papers, that we employed to obtain many bicyclic imidazo-derivatives. Such method is based on the reaction of a heteroarylamine with an α-haloketoester: for instance, the reaction in ethanolic solution of 2-aminopyridine with ethyl 2-benzoyl-2-bromoacetate **1** afforded ethyl 2-phenylimidazo[1,2-*a*]-pyridine-3-carboxylate **2** (Figure 3).

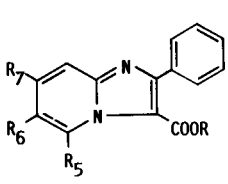


1 2

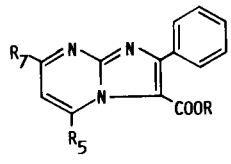
Figure 3

Starting from the suitable amines we synthesized three imidazo[1,2-*a*]pyridines, namely the ethyl carboxylates **2, 3** and **4** and three imidazo[1,2-*a*]pyrimidines, namely the ethyl carboxylates **5, 6** and **7**, which are all listed in Figure 4. The structures assigned to these compounds were unequivocally supported by elemental analytical data and ^1H nmr spectra, which were in good accordance with both available literature data on imidazo[1,2-*a*]pyridines [9-11] and imidazo[1,2-*a*]pyrimidines [12,13], respectively, and our previously reported experimental data [1,2].

The reaction of the bromoketoester **1** with the suitable aminothiazole and aminobenzothiazole derivatives afforded compounds **8-11** (Figure 5), whose structures were in turn unequivocal on the basis of experimental data which were in close accordance with preceding experimental evidence [6,7].

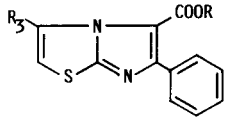


2 : R = C_2H_5; R_5,R_6,R_7 = H
3 : R = C_2H_5; R_6 = CH_3; R_5,R_7 = H
4 : R = C_2H_5; R_6 = H; R_5,R_7 = CH_3
16 : R,R_5,R_6,R_7 = H
17 : R,R_5,R_7 = H; R_6 = CH_3

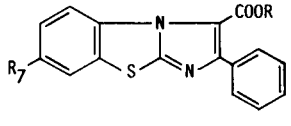


5 : R = C_2H_5; R_5,R_7 = H
6 : R = C_2H_5; R_5 = H; R_7 = CH_3
7 : R = C_2H_5; R_5,R_7 = CH_3
18 : R,R_5,R_7 = H
19 : R,R_5 = H; R_7 = CH_3

Figure 4



8 : R = C_2H_5; R_3 = CH_3
9 : R = C_2H_5; R_3 = H
20 : R = H; R_3 = CH_3
21 : R,R_3 = H

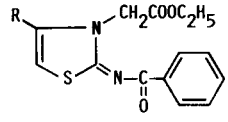


10 : R = C_2H_5; R_7 = H
11 : R = C_2H_5; R_7 = OC_2H_5
22 : R,R_7 = H

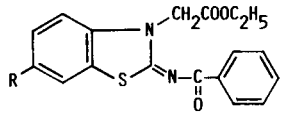
Figure 5

It has to be pointed out that, when the starting amine was a thiazole or benzothiazole derivative, the required product was accompanied by a comparable amount of an unexpected compound, whereas only the required products depicted in Figure 4 were obtained starting from aminopyridines and aminopyrimidines.

For example, the reaction of 2-amino-4-methylthiazole with the bromoketoester **1** afforded ethyl 3-methyl-6-phenylimidazo[2,1-*b*]thiazole-5-carboxylate **8** together with another product to which structure **12** (Figure 6) was assigned as follows.



12 : R = CH_3
13 : R = H

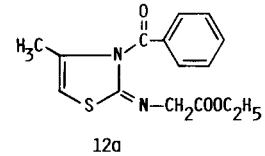


14 : R = H
15 : R = OC_2H_5

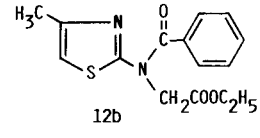
Figure 6

Compound **12** had molecular formula $C_{15}H_{16}N_2O_3S$ (from high resolution mass spectroscopy and elemental analysis). The presence of a $-COOC_2H_5$ function was established from ir (ν max cm^{-1} 1750 and 1285), ^1H nmr [δ 4.26 (q, 2H, J = 6.5 Hz) and 1.29 (t, 3H, J = 6.5 Hz)] and ^{13}C nmr [δ 167.0 (C=O), 61.6 (OCH_2) and 13.8 (CH_3)] spectra, while a monosubstituted benzene group was apparent from the pertinent signals in the ^1H nmr [δ 8.30 (m, 2H) and 7.45 (m, 3H)] and ^{13}C nmr [δ 136.6 (-C≤), 131.1 (*para* -CH=), 128.9 (two *ortho* -CH=) and 127.6 (two *meta* -CH=)] spectra. Furthermore compound **12** must possess both a methyl group linked to a trisubstituted carbon-carbon double bond and an isolated methylene group as indicated by the presence of the corresponding resonances at δ 2.29 (broad s, 3H), 4.96 (s, 2H) and 6.31 (broad s, 1H) in the ^1H nmr spectrum and at δ 13.45 ($-CH_3$), 46.7 ($-CH_2-$) and 103.8 (-CH=) in the ^{13}C nmr spectrum. Finally, the ^{13}C nmr spectrum comprised also signals due to two further fully substituted sp^2 carbons which, on the basis of their chemical shifts (δ 173.4 and 168.8), must be linked to heteroatoms.

The overall above data clearly indicated the alternative formulae **12** (Figure 6), **12a** and **12b** (Figure 7) as the most plausible for the side product under examination. The hypothetical structures **12a** and **12b** could be ruled out on the basis of ^{13}C-^1H shift correlated 2D-nmr spectrum *via* ^2J and ^3J as indicated in Figure 8, which confirmed the above attributions and led to unambiguous positioning of the methylene group, whose protons were observed to correlate with C-4. In conclusion, the unexpected product obtained starting from 2-amino-4-methylthiazole is ethyl 2-benzoylimino-2,3-dihydro-4-methylthiazole-3-acetate **12**.

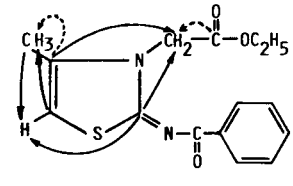


12a



12b

Figure 7



12

Figure 8

Table I

NMR Data for C and D Moieties (see Figure 9) of 12-15

Compound	NMR	Chemical Shift Assignment (δ) for the Carbon and Hydrogen Atoms Indicated									
		a	b	c	d	e	f	g	h	i	j
12	^1H	–	–	–	8.30	7.45	7.45	4.96	–	4.26	1.29
	^{13}C	168.8	173.4	136.6	128.9	127.6	131.1	46.7	167.0	61.6	13.8
13	^1H	–	–	–	8.30	7.42	7.42	4.96	–	4.24	1.30
	^{13}C	168.2	173.9	136.7	129.3	127.9	131.5	49.3	166.9	62.0	14.0
14	^1H	–	–	–	8.35	7.50	7.50	5.26	–	4.28	1.30
	^{13}C	168.0	175.0	136.5	129.7	128.1	132.0	46.5	166.7	62.0	14.1
15	^1H	–	–	–	8.35	7.48	7.48	5.20	–	4.26	1.30
	^{13}C	156.8	160.6	134.7	129.9	127.5	128.4	46.5	154.2	60.8	13.8

The structure determination for compounds **13**, **14** and **15** (Figure 6), which were the by-products accompanying the required products **9**, **10** and **11**, respectively, was essentially based on the comparison of their spectral features with those of **12**. Particularly, each of them derived from the starting materials by elimination of a hydrogen bromide molecule, as deduced by ms data. Moreover, ir absorptions at ν max 1750 and 1285 cm^{-1} and both ^1H and ^{13}C nmr spectral data (reported in Table I) clearly indicated that they incorporate the same moieties **C** and **D** (Figure 9). Apparent discrepancies observed in some values can be readily explained.

The downfield shift of C_g in **13** is attributable to the absence of any substituent at C-4 of the thiazole ring and consequent lacking of a γ-effect. On the other hand, the difference in the chemical shifts of the methylenic protons of C_g in **14** and **15** when compared with those of **12** and **13**

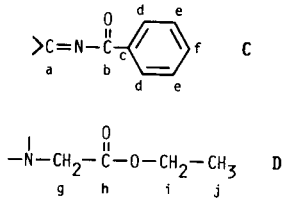


Figure 9

are clearly due to the effect of the aromatic ring.

A plausible mechanism which accounts for the formation of compounds **12-15** is depicted in Figure 10. Accordingly with this hypothesis, the key intermediate **E** evolves through elimination of a water molecule to give the main product **F**. Alternatively, a retro-aldol type reaction on **E** could afford compound **G**.

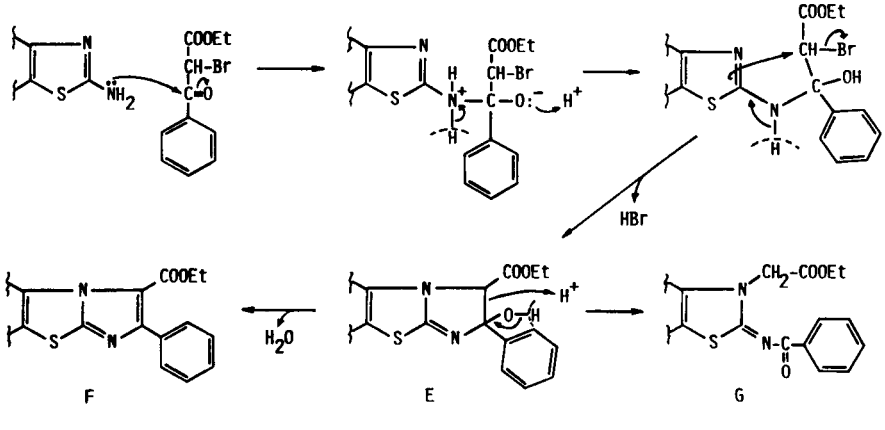


Figure 10

The ethyl carboxylates **2**, **3**, **5**, **6**, **8**, **9** and **10** underwent alkaline hydrolysis to afford the corresponding carboxylic acids **16-22** (Figure 4-5), whereas the other ethyl esters **4**, **7** and **11** were obtained in too much low yield to allow the preparation of the corresponding acids in sufficient amounts for pharmacological testing.

It has to be pointed out that the ethyl ester **9** was already reported in a patent in form of hydrochloride and hydrobromide [14]; the acid **22** was cited in another patent [15]. The acid **21** was synthesized by Andreani *et al.* [16] by means of a different synthetic method.

The results obtained in the pharmacological testing of compounds **16-22** will be reported and discussed elsewhere.

EXPERIMENTAL

Precoated silica gel Whatman K6F plates were used for thin layer chromatography; detection of components was made by either uv light or treatment with iodine vapors. Chromatographic separations were performed on columns packed with silica gel 60 from Merck, 70-230 mesh ASTM. Melting points were determined with a Kofler hot stage microscope and are uncorrected. Elemental analyses were performed by a Perkin-Elmer Elemental Analyzer Model 240 and were within ±0.4% of the calculated values. The ir spectra were recorded with a Perkin-Elmer 399 spectrometer in chloroform solutions. The ^1H and ^{13}C nmr spectra were obtained with a Bruker WM250 spectrometer. Two-dimensional ^{13}C-^1H shift correlation *via* ^2J and ^3J (COLOC) was performed with the aid of a Bruker microprogram adjusting the fixed delays to give the maximum polarization transfer for $J_{C\text{-}H}$ = 6.25 Hz. Low resolution mass spectra were recorded at 70 eV on a AEI MS 30 mass spectrometer. High resolution mass spectra were recorded on a AEI MS 902 spectrometer. Commercially available solvents and chemicals were used for syntheses, with the exception of ethyl 2-benzoyl-2-bromoacetate **1** which was prepared by bromination of ethyl benzoylacetate following Cooper *et al.* [17].

Ethyl 2-Phenylimidazo[1,2-*a*]pyridine-3-carboxylate (**2**).

A solution of 2.6 g (0.027 mole) of 2-aminopyridine and 7.3 g (0.027 mole) of ethyl 2-benzoyl-2-bromoacetate **1** in 80 ml of anhydrous ethanol was refluxed for 4 hours. The solution was then evaporated under reduced pressure. The residue was dissolved in sodium hydrogen carbonate saturated solution and extracted three times with chloroform. The extracts were combined, washed with water, dried on anhydrous sodium sulfate, concentrated *in vacuo* up to a small volume and then chromatographed on a silica gel column, eluting initially with chloroform and then with chloroform-methanol (98:2). Fractions containing the required product were combined, the solvent was removed *in vacuo* and the residue was recrystallized from *n*-hexane to obtain 2.1 g (yield 29%) of colorless crystals, mp 78-80°; ^1H nmr (deuteriochloroform): δ 9.44 (splitting d, 1H, H-5), 7.78 (m, 3H) and 7.45 (m, 4H) (H-7, H-8 and phenyl protons), 7.07 (splitting t, 1H, H-6), 4.33 (q, 2H, $-CH_2-$), 1.24 (t, 3H, $-CH_3$), $J_{5,6}$ = 6.5 Hz.

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.97; H, 5.27; N, 10.56.

Closely similar procedures were employed to obtain the other following ethyl esters **3-7**.

Ethyl 6-Methyl-2-phenylimidazo[1,2-*a*]pyridine-3-carboxylate (**3**).

The starting amine was 2-amino-5-methylpyridine, yield 55%, mp 75-77° (*n*-hexane); ^1H nmr (deuteriochloroform): δ 9.17 (d, 1H, H-5), 7.70 (m, 2H) and 7.37 (m, 3H) (phenyl protons), 7.56 (d, 1H, H-8), 7.20 (dd, 1H, H-7), 4.23 (q, 2H, $-CH_2-$), 2.34 (s, 3H, 6-CH_3), 1.15 (t, 3H, ethyl $-CH_3$), $J_{7,8}$ = 9.4 Hz, $J_{5,7}$ = 1.5 Hz.

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.88; H, 5.65; N, 9.88.

Ethyl 5,7-Dimethyl-2-phenylimidazo[1,2-*a*]pyridine-3-carboxylate (**4**).

The starting amine was 2-amino-4,6-dimethylpyridine, yield 6%, oil; ^1H nmr (deuteriochloroform): δ 7.75 (m, 2H, two phenyl protons), 7.41 (m, 4H, three phenyl protons and H-8), 6.62 (s, 1H, H-6), 4.26 (q, 2H, $-CH_2-$), 2.63 and 2.42 (two s, 3H each, 5- and 7-CH_3), 1.18 (t, 3H, ethyl $-CH_3$).

Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.22; H, 6.04; N, 9.50.

Ethyl 2-Phenylimidazo[1,2-*a*]pyrimidine-3-carboxylate (**5**).

The starting amine was 2-aminopyrimidine, yield 16%, mp 125-127° (*n*-hexane/carbon tetrachloride); ^1H nmr (deuteriochloroform): δ 9.69 (dd, 1H, H-5), 8.74 (dd, 1H, H-7), 7.87 (m, 2H) and 7.46 (m, 3H) (phenyl protons), 7.12 (dd, 1H, H-6), 4.36 (q, 2H, $-CH_2-$), 1.27 (t, 3H, $-CH_3$), $J_{5,6}$ = 7 Hz, $J_{6,7}$ = 4 Hz, $J_{5,7}$ = 2 Hz.

Anal. Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.58; H, 4.95; N, 15.57.

Ethyl 7-Methyl-2-phenylimidazo[1,2-*a*]pyrimidine-3-carboxylate (**6**).

The starting amine was 2-amino-4-methylpyrimidine, yield 32%, mp 108-110° (petroleum ether/carbon tetrachloride 2:1); ^1H nmr (deuteriochloroform): δ 8.88 (d, 1H, H-5), 7.89 (m, 2H) and 7.45 (m, 3H) (phenyl protons), 6.98 (d, 1H, H-6), 4.34 (q, 2H, $-CH_2-$), 2.71 (s, 3H, 7-CH_3), 1.27 (t, 3H, ethyl $-CH_3$), $J_{5,6}$ = 7 Hz.

Anal. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.38; N, 14.94. Found: C, 68.05; H, 5.30; N, 15.01.

Ethyl 5,7-Dimethyl-2-phenylimidazo[1,2-*a*]pyrimidine-3-carboxylate (**7**).

The starting amine was 2-amino-4,6-dimethylpyrimidine, yield 3%, mp 80-82° (*n*-hexane); ^1H nmr (deuteriochloroform): δ 7.84 (m, 2H) and 7.44 (m, 3H) (phenyl protons), 6.72 (s, 1H, H-6), 4.28 (q, 2H, $-CH_2-$), 2.69 and 2.64 (two s, 3H each, 5- and 7-CH_3), 1.21 (t, 3H, ethyl $-CH_3$).

Anal. Calcd. for $C_{17}H_{17}N_3O_2$: C, 69.13; H, 5.80; N, 14.23. Found: C, 68.98; H, 5.78; N, 14.05.

Ethyl 3-Methyl-6-phenylimidazo[2,1-*b*]thiazole-5-carboxylate (**8**).

A solution of 3.42 g (0.03 mole) of 2-amino-4-methylthiazole and 8.15 g (0.03 mole) of **1** in 80 ml of anhydrous ethanol was refluxed for 10 hours. The solution was then evaporated *in vacuo*. The residue was treated with sodium hydrogen carbonate saturated solution and extracted with chloroform. The organic layer was washed with water, dried on anhydrous sodium sulfate and evaporated up to a small volume: this concentrated solution was chromatographed on a silica gel column using chloroform-petroleum ether (7:3) to elute the initial fractions, then mixtures with decreasing percentage of petroleum ether and finally chloroform alone. Such chromatographic procedure eliminated the unre-

acted starting products and other impurities to afford a mixture of **8** and **12**. This mixture was then resolved in its two components by means of a second silica gel column, which was in turn eluted with diethyl ether-petroleum ether mixtures (initially 7:3) with decreasing amounts of petroleum ether up to diethyl ether alone. This couple of chromatographic procedures allowed us to isolate 0.4 g (yield 4.6%) of the required product **8**, mp 97-99° (from *n*-hexane); ^{1}H nmr (deuteriochloroform): δ 7.70 (m, 2H) and 7.38 (m, 3H) (phenyl protons), 6.44 (s, 1H, H-2), 4.22 (q, 2H, $-CH_2-$), 2.58 (s, 3H, 3-CH_3), 1.15 (t, 3H, ethyl CH_3).

Anal. Calcd. for $C_{15}H_{14}N_2O_2S$: C, 62.92; H, 4.93; N, 9.78. Found: C, 62.90; H, 4.89; N, 9.80.

Ethyl 2-Benzoylimino-2,3-dihydro-4-methylthiazole-3-acetate (**12**).

The title product was separated from **8** and isolated by the above chromatographic procedure to obtain 0.7 g (yield 7.7%) of **12** in form of colorless crystals, mp 119-121° (from *n*-hexane); ir (chloroform): ν max 1750, 1285 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.30 (m, 2H) and 7.45 (m, 3H) (phenyl protons), 6.31 (broad s, 1H, H-5), 4.96 (s, 2H, acetate $-CH_2-$), 4.26 (q, 2H, ethyl $-CH_2$), 2.29 (broad s, 3H, 4-CH_3), 1.29 (t, 3H, ethyl CH_3), J_{CH_2,CH_3} = 6.5 Hz; ^{13}C nmr (deuteriochloroform): δ 173.4 (NCO, b), 168.8 (thiazole C-2, a), 167.0 (COO, h), 136.6 (phenyl quaternary C, c), 133.5 (thiazole C-4), 131.1 (*para* phenyl CH, f), 128.9 (two *ortho* phenyl CH, d), 127.6 (two *meta* phenyl CH, e), 103.8 (thiazole 5-CH), 61.6 (OCH_2, i), 46.7 (NCH_2, g), 13.8 (ethyl CH_3, j), 13.45 (4-CH_3); ms: m/e 304 (M^+, 31%), 227 ($M^+-C_6H_5$, 26%), 199 ($M^+-C_6H_5CO$, 8%), 105 (C_6H_5CO, base peak), 77 (C_6H_5, 70%); hrms: found m/e 304.3335, $C_{15}H_{16}N_2O_3S$ requires 304.3646.

Anal. Calcd. for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.20. Found: C, 59.15; H, 5.32; N, 9.25.

Ethyl 6-Phenylimidazo[2,1-*b*]thiazole-5-carboxylate (**9**).

A solution of 4 g (0.04 mole) of 2-aminothiazole and 10.8 g (0.04 mole) of **1** in 100 ml of anhydrous ethanol was refluxed for 6 hours. The reacted solution was worked up in the same manner already described for **8**, using chloroform to elute the first chromatographic column and diethyl ether for the second one to afford 1.3 g (yield 12%) of the required product **9**, mp 68-70° (from *n*-hexane); ^{1}H nmr (deuteriochloroform): δ 8.20 (d, 1H, H-3), 7.86 (m, 2H) and 7.43 (m, 3H) (phenyl protons), 6.98 (d, 1H, H-2), 4.35 (q, 2H, $-CH_2-$), 1.31 (t, 3H, $-CH_3$), $J_{2,3}$ = 4.5 Hz.

Anal. Calcd. for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29. Found: C, 61.65; H, 4.41; N, 10.20.

Ethyl 2-Benzoylimino-2,3-dihydrothiazole-3-acetate (**13**).

This product was separated from **9** and isolated by the above chromatographic procedure, obtaining 1.7 g (yield 15%) of colorless crystals, mp 100-102° (from *n*-hexane/carbon tetrachloride 2:1); ir (chloroform): ν max 1750, 1285 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.30 (m, 2H) and 7.42 (m, 3H) (phenyl protons), 7.01 (d, 1H, H-4), 6.67 (d, 1H, H-5), 4.96 (s, 2H, acetate $-CH_2-$), 4.24 (q, 2H, ethyl $-CH_2-$), 1.30 (t, 3H, $-CH_3$); ^{13}C nmr (deuteriochloroform): δ 173.9 (NCO, b), 168.2 (thiazole C-2, a), 166.9 (COO, h), 136.7 (phenyl quaternary C, c), 131.5 (*para* phenyl CH, f), 129.3 (two *ortho* phenyl CH, d), 127.9 (two *meta* phenyl CH, e), 125.9 (thiazole 4-CH), 108.75 (thiazole 5-CH), 62.0 (OCH_2, i), 49.3 (NCH_2, g), 14.0 (CH_3, j); ms: m/e 290 (M^+, 73%), 262 ($M^+-C_2H_4$, 18%), 245 ($M^+-C_2H_5O$, 10%), 213 ($M^+-C_6H_5$, 70%), 185 ($M^+-C_6H_5CO$, 30%), 140 ($M^+-C_6H_5CO-C_2H_5O$, 15%), 105 (C_6H_5CO, base peak), 77 (C_6H_5, 90%).

Anal. Calcd. for $C_{14}H_{14}N_2O_3S$: C, 57.92; H, 4.86; N, 9.65. Found: C, 57.78; H, 4.77; N, 9.50.

Ethyl 2-Phenylimidazo[2,1-*b*]benzothiazole-3-carboxylate (**10**).

A solution of 4.5 g (0.03 mole) of 2-aminobenzothiazole and 8.15 g (0.03 mole) of **1** in 100 ml of anhydrous ethanol was refluxed for 10 hours. The solution was then evaporated under reduced pressure. The residue was dissolved in sodium hydrogen carbonate saturated solution and extracted with chloroform. The extract was washed with water, dried on anhydrous sodium sulfate and evaporated to dryness *in vacuo*. The residue was dissolved in hot *n*-hexane/carbon tetrachloride mixture (1:1), from which the unreacted starting amine crystallized out; the filtrate was concentrated under reduced pressure up to a small volume and then chromatographed on a silica gel column eluting with chloroform. The fractions containing the required product were combined and evaporated to dryness *in vacuo*; the residue was recrystallized from *n*-hexane to give 2.2 g (yield 23%) of **10**, mp 112-114°; ^{1}H nmr (deuteriochloroform): δ 8.86 (splitting d, 1H), 7.75 (m, 3H) and 7.45 (m, 5H) (aromatic protons), 4.33 (q, 2H, $-CH_2-$), 1.22 (t, 3H, $-CH_3$).

Anal. Calcd. for $C_{18}H_{14}N_2O_2S$: C, 67.06; H, 4.38; N, 8.69. Found: C, 66.84; H, 4.31; N, 8.70.

Ethyl 2-Benzoylimino-2,3-dihydrobenzothiazole-3-acetate (**14**).

The above chromatographic procedure gave 2.45 g (yield 24%) of **14**, mp 165-167° (from *n*-hexane/carbon tetrachloride 2:1); ir (chloroform): ν max 1750, 1290 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.35 (m, 2H), 7.75 (splitting d, 1H), 7.50 (m, 4H), 7.35 (t, 1H) and 7.26 (splitting d, 1H) (aromatic protons), 5.26 (s, 2H, acetate $-CH_2-$), 4.28 (q, 2H, ethyl $-CH_2-$), 1.30 (t, 3H, $-CH_3$); ^{13}C nmr (deuteriochloroform): δ 175.0 (NCO, b), 168.0 (thiazole C-2, a), 166.7 (COO, h), 136.54 (phenyl quaternary C, c), 136.46 and 126.7 (C-3a and C-7a), 132.0 (*para* phenyl CH, f), 129.7 (two *ortho* phenyl CH, d), 128.1 (two *meta* phenyl CH, e), 127.0, 124.1, 123.1 and 110.8 (4,5,6,7-CH), 62.0 (OCH_2, i), 46.5 (NCH_2, g), 14.1 (CH_3, j); ms: m/e 340 (M^+, 25%), 312 ($M^+-C_2H_4$, 10%), 263 ($M^+-C_6H_5$, 30%), 235 ($M^+-C_6H_5CO$, 10%), 105 (C_6H_5CO, base peak), 77 (C_6H_5, 95%).

Anal. Calcd. for $C_{18}H_{16}N_2O_3S$: C, 63.51; H, 4.74; N, 8.23. Found: C, 63.60; H, 4.76; N, 8.23.

Ethyl 7-Ethoxy-2-phenylimidazo[2,1-*b*]benzothiazole-3-carboxylate (**11**).

A solution of 5.8 g (0.03 mole) of 2-amino-6-ethoxybenzothiazole and 8.15 g (0.03 mole) of **1** in 100 ml of anhydrous ethanol was refluxed for 14 hours. The reacted solution was worked up as already described for **8**; the first chromatographic column was eluted with chloroform, whereas the second column was eluted with dichloromethane to afford 0.9 g (yield 8%) of **11**, mp 155-157° (from *n*-hexane); ^{1}H nmr (deuteriochloroform): δ 8.77 (d, 1H, H-5), 7.70 (m, 2H) and 7.43 (m, 3H) (phenyl protons), 7.20 (d, 1H, H-8), 7.04 (dd, 1H, H-6), 4.32 (q, 2H) and 4.12 (q, 2H) ($-CH_2-$ groups), 1.48 (t, 3H) and 1.20 (t, 3H) ($-CH_3$ groups), $J_{5,6}$ = 8.5 Hz, $J_{6,8}$ = 2.5 Hz.

Anal. Calcd. for $C_{20}H_{18}N_2O_3S$: C, 65.55; H, 4.95; N, 7.64. Found: C, 65.66; H, 4.95; N, 7.59.

Ethyl 2-Benzoylimino-2,3-dihydro-6-ethoxybenzothiazole-3-acetate (**15**).

The chromatographic procedure described in the above paragraph afforded also 2.87 g (yield 25%) of **15**, mp 177-178° (from carbon tetrachloride); ir (chloroform): ν max 1750, 1280 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.35 (m, 2H) and 7.48 (m, 3H) (phenyl protons), 7.30 (d, 1H, H-4), 7.15 (d, 1H, H-7), 7.04 (dd, 1H, H-5), 5.20 (s, 2H, acetate $-CH_2-$), 4.26 (q, 2H) and 4.06 (q, 2H) (ethyl $-CH_2-$ groups), 1.45 (t, 3H) and 1.30 (t, 3H) ($-CH_3$ groups), $J_{4,5}$ = 9 Hz, $J_{5,7}$ = 2.5 Hz; ^{13}C nmr (deuteriochloroform): δ 160.6 (NCO, b), 156.8 (thiazole C-2, a), 154.2 (COO, h), 134.7 (phenyl quaternary C, c), 131.5 and 128.0 (C-3a and C-7a), 129.9 (two *ortho* phenyl CH, d), 129.6 (C-6); 128.4 (*para* phenyl CH, f), 127.5 (two *meta* phenyl CH, e), 118.4, 114.1 and 108.6 (4,5,7-CH); 64.3 (6-OCH_2), 60.8 (ethyl OCH_2, i), 46.5 (NCH_2, g), 14.7 (6-ethoxyl CH_3), 13.8 (ethyl CH_3, j); ms: m/e 384 (M^+, 15%), 307 ($M^+-C_6H_5$, 9%), 105 (base peak, C_6H_5CO), 77 (C_6H_5, 58%).

Anal. Calcd. for $C_{20}H_{20}N_2O_4S$: C, 62.48; H, 5.24; N, 7.29. Found: C, 62.35; H, 5.19; N, 7.34.

2-Phenylimidazo[1,2-*a*]pyridine-3-carboxylic Acid (**16**).

A solution of 2 g of the ethyl ester **2** in 30 ml of 2*N* sodium hydroxide solution in 80% aqueous ethanol was heated at 60° for one hour. Ethanol was then removed under reduced pressure and the concentrated solution was adjusted to *p*H 4 with diluted hydrochloric acid. The precipitate obtained was filtered and recrystallized from ethanol to afford 1.3 g (yield 72%) of **16**, mp 132° dec; ^1H nmr (dimethyl sulfoxide-d_6): δ 9.40 (splitting t, 1H, H-5), 7.79 (m, 3H), 7.59 (m, 1H) and 7.45 (m, 3H) (H-7, H-8 and phenyl protons), 7.23 (splitting t, 1H, H-6).

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.39; H, 4.17; N, 11.61.

The same procedure described for **16** was employed to obtain the other following carboxylic acids.

6-Methyl-2-phenylimidazo[1,2-*a*]pyridine-3-carboxylic Acid (**17**).

The starting ethyl ester was **3**, yield 60%, mp 206-208° dec; ^1H nmr (trifluoroacetic acid-d): δ 7.55 (d, 1H, H-5), 7.24 (d, 1H, H-8), 7.04 (dd, 1H, H-7), 6.95 (m, 2H) and 6.75 (m, 3H) (phenyl protons), 2.58 (s, 3H, $-CH_3$), $J_{7,8}$ = 9.5 Hz, $J_{5,7}$ = 1.5 Hz.

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.28; H, 4.81; N, 11.00.

2-Phenylimidazo[1,2-*a*]pyrimidine-3-carboxylic Acid (**18**).

The starting ethyl ester was **5**, yield 64%, mp 174-176° dec; ^1H nmr (dimethyl sulfoxide-d_6): δ 9.68 (dd, 1H, H-5), 8.80 (dd, 1H, H-7), 7.87 (m, 2H) and 7.49 (m, 3H) (phenyl protons), 7.35 (dd, 1H, H-6), $J_{5,6}$ = 7 Hz, $J_{6,7}$ = 4 Hz, $J_{5,7}$ = 2 Hz.

Anal. Calcd. for $C_{13}H_9N_3O_2$: C, 65.26; H, 3.79; N, 17.57. Found: C, 64.99; H, 3.65; N, 17.66.

7-Methyl-2-phenylimidazo[1,2-*a*]pyrimidine-3-carboxylic Acid (**19**).

The starting ethyl ester was **6**, yield 53%, mp 228-230° dec; ^1H nmr (dimethyl sulfoxide-d_6): δ 9.48 (d, 1H, H-5), 7.84 (m, 2H) and 7.46 (m, 3H) (phenyl protons), 7.23 (d, 1H, H-6), 2.60 (s, 3H, $-CH_3$), $J_{5,6}$ = 7 Hz.

Anal. Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.39; H, 4.38; N, 16.59. Found: C, 66.40; H, 4.33; N, 16.60.

3-Methyl-6-phenylimidazo[2,1-*b*]thiazole-5-carboxylic Acid (**20**).

The starting ethyl ester was **8**, yield 49%, mp 150° dec; ^1H nmr (deuteriochloroform): δ 7.68 (m, 2H) and 7.50 (m, 3H) (phenyl protons), 6.98 (s, 1H, H-2), 2.58 (s, 3H, $-CH_3$).

Anal. Calcd. for $C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.90; N, 10.84. Found: C, 60.15; H, 3.80; N, 10.90.

6-Phenylimidazo[2,1-*b*]thiazole-5-carboxylic Acid (**21**).

The starting ethyl ester was **9**, yield 59%, mp 152-154° dec; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.23 (d, 1H, H-3), 7.85 (m, 2H) and 7.42 (m, 3H) (phenyl protons), 7.50 (d, 1H, H-2), $J_{2,3}$ = 4.5 Hz.

Anal. Calcd. for $C_{12}H_8N_2O_2S$: C, 59.00; H, 3.30; N, 11.47. Found: C, 58.87; H, 3.30; N, 11.41.

2-Phenylimidazo[2,1-*b*]benzothiazole-3-carboxylic Acid (**22**).

The starting ethyl ester was **10**, yield 54%, mp 211-213° dec; ^1H nmr (trifluoroacetic acid-d): δ 7.90 (d, 1H), 6.90 (d, 1H) and 6.55 (m, 7H) (aromatic protons).

Anal. Calcd. for $C_{16}H_{10}N_2O_2S$: C, 65.29; H, 3.42; N, 9.52. Found: C, 65.10; H, 3.40; N, 9.50.

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