Friedländer Reaction of 3-Acetyltropolones: Synthesis of Naphthyridinyl- and Allied Heterocyclic-Substituted Tropolones

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Five 3-acetyltropolones reacted with 2-amino-3-pyridinecarbaldehyde to afford the corresponding 3-(1,8-naphthyridin-2-yl)tropolones in excellent yields. In a similar manner, 1,6-naphthyridin-2-yl-, 1,7-naphthyridin-2-yl-, 6-pyrido[2,3-*b*]pyrazinyl-, and 1-methyl-6-pyrazolo[5,4-*b*]pyridyl-substituted tropolones were prepared. Reactivities of amino-substituted heteroarenecarbaldehydes in these reactions and properties of the products are also discussed.

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We have reported synthesis of a number of heterocyclic-fused tropoid compounds utilizing the positional features of the acetyl group [1]. On the other hand, little is known about tropolones possessing a heterocyclic ring as the substituents except for several compounds, such as 4-(3- and 5-pyrazolyl)- [2,3], 4-(5-isoxazolyl)- [3], 3-(4-thiazolyl)- [4,5], and 4-(2-quinolyl)tropolones [6].

Recently, we applied Friedländer reaction [7,8] to 3-acetyltropolone and found that reactions with 2-aminobenzaldehydes are useful for synthesis of 3-(2-quinolyl)tropolones [9]. On the extension of this reaction, we wish to describe synthesis of tropolones possessing bicyclic ring with two and more nitrogen atoms. These synthetic reactions are directed to further synthetic utility of 3-acetyltropolone and creative development of biologically active compounds.

Results and Discussion.

Reactions of 3-Acetyltropolones **1a-e** with Aminopyridinecarbaldehydes.

The Friedländer reaction is initiated by attack of a carbanion formed from an active methylene or methyl group neighboring to the carbonyl function on the formyl carbon atom of 2-aminobenzaldehydes followed by cyclization to afford the quinoline skeleton.

The reactions of 3-acetyltropolones **1a-e** with 2-amino-3-pyridinecarbaldehyde (**2**) were carried out. Compound **2** is expected to be more reactive than aminobenzaldehydes, because the pyridine ring is more electron-deficient than the benzene ring. The reaction of 3-acetyltropolone (**1a**) with aminopyridinecarbaldehyde **2** afforded 3-(1,8-naphthyridin-2-yl)tropolone (**3a**). In order to optimize the reaction, we examined the reaction conditions such as base, solvent, temperature, *etc.* The results are listed in Table 1.

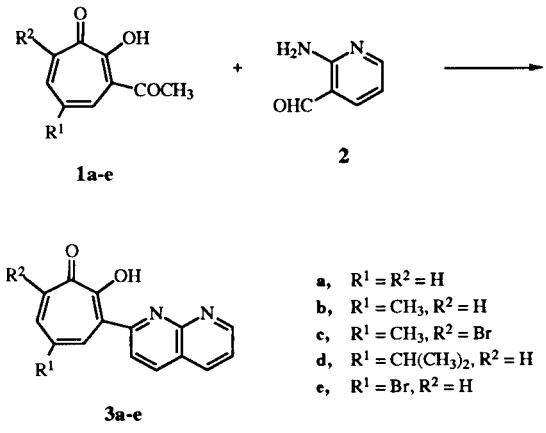
Table 1

Reactions of 3-Acetyltropolone (**1a**) with 2-Amino-3-pyridinecarbaldehyde (**2**)

Entry	Base	Solvent	Molar ratio [a]	Temp [b] (°C)	Time (h)	Product **3a** [Yield/%]	Compound **1a** [Recovery/%]
1	NaOH	50% CH_3OH	1:1:1	RT	72	—	96
2	NaOH	50% CH_3OH	1:1:2	RT	24	38	53
3	NaOH	50% CH_3OH	1:1:2	65	24	76	16
4	KOH	50% CH_3OH	1:1:1	65	26	—	92
5	KOH	50% CH_3OH	1:1:2	65	22	74	12
6	KOH	50% CH_3OH	1:1.5:2	65	24	96	2
7	KOH	H_2O	1:1:2	RT	24	74	13
8	KOH	H_2O	1:1:2	65	24	89	6
9	$NaOC_2H_5$	C_2H_5OH	1:1:2	RT	24	76	19
10	$NaOC_2H_5$	C_2H_5OH	1:1.1:2	90	1	74	11
11	Na_2CO_3	50% CH_3OH	1:1.1:4	100	24	93	4
12	K_2CO_3	50% CH_3OH	1:1.1:4	100	24	91	7
13	$(CH_3)_4NOH$	50% CH_3OH	1:1:2	65	24	73	14
14	Piperidine	CH_3OH	1:1:2	65	26	58	32
15	H_2SO_4 [c]	CH_3COOH	1:1:3	65	60	—	95

[a] **1a**:**2**:Base. [b] Bath temperature. [c] Acid additive.

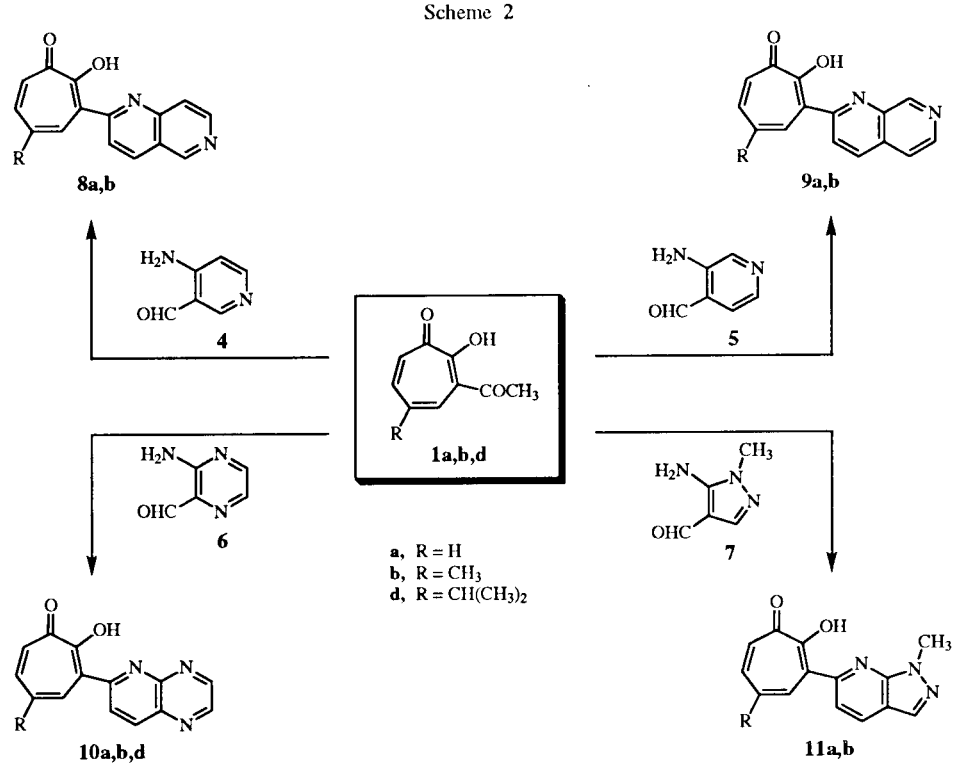
Scheme 1



sodium ethoxide, gave good results even at room temperature (Entry 9) and an excellent yield at 90° after only 1 hour (Entry 10). In the use of even a weak base, such as sodium carbonate and potassium carbonate, the excellent results were obtained at 100° in the presence of four equivalents of the base (Entries 11 and 12). The reactions in the presence of tetramethylammonium hydroxide and piperidine gave **3a** in moderate yields (Entries 13 and 14). However, an acid additive gave no product at all (Entry 15). Consequently, it was found that the reaction in Entry 6 gave the best result.

According to the reaction condition in Entry 6, the reactions of 3-acetyltropolones **1b-e** were carried out to give the corresponding 3-(1,8-naphthyridin-2-yl)tropolones **3b-e** in very high yields (**3b**, 87%; **3c**, 87%; **3d**, 91%; **3e**, 96%).

Scheme 2



The reaction using an equimolar amount of base gave no product, while the starting material **1a** was recovered almost quantitatively (Entries 1 and 4). Thus, two or more equivalents of the base should be used, because an equimolar amount of the base might be presumably consumed for neutralization of the acidic tropolone **1a** to afford its salt. Using two molar equivalents of the base, the reactions at elevated temperature (65°) gave 3-(1,8-naphthyridin-2-yl)tropolone (**3a**) in high yields (Entries 3, 5, and 8). Additionally, the reaction with one and half equivalents of **2** gave the compound **3a** in an excellent yield (Entry 6). The reactions using a strong base,

We then tried the reactions with a series of amino-substituted heteroarenecarbaldehydes, such as 4-amino-3-pyridinecarbaldehyde (**4**), 3-amino-4-pyridinecarbaldehyde (**5**), 3-amino-2-pyrazinecarbaldehyde (**6**), and 5-amino-1-methyl-4-pyrazolecarbaldehyde (**7**) in a similar manner. When a solution of 3-acetyltropolones **1a,b** and an equimolar amount of 4-amino-3-pyridinecarbaldehyde (**4**) was heated for 17 hours at 65° in the presence of two equivalents of potassium hydroxide 3-(1,6-naphthyridin-2-yl)tropolones **8a,b** in 88 and 90% yield were obtained, respectively. The reactions of **1a,b** with 3-amino-4-pyridinecarbaldehyde (**5**) in the same way gave 3-(1,7-

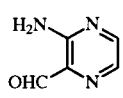
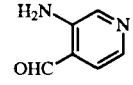
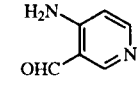
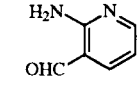
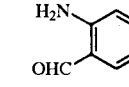
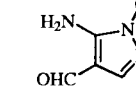
naphthyridin-2-yl)tropolones **9a,b** in excellent yields (**9a**, 90%; **9b**, 92%). Since the pyrazine ring is more electron-deficient than the pyridine ring, the reactions of 3-acetyltropolones **1a,b,d** with 3-amino-2-pyrazinecarbaldehyde (**6**) took place even at room temperature with stirring for 24 hours to afford 3-(6-pyrido[2,3-*b*]pyrazinyl)tropolones **10a,b,d** in high yields (**10a**, 91%; **10b**, 90%; **10d**, 74%). On the other hand, a five-membered pyrazole ring is more electron-rich than six-membered rings. When the reactions of **1a,b** with 5-amino-1-methyl-4-pyrazolecarbaldehyde (**7**) were run under reflux conditions for 1 hour in the presence of a stronger base, sodium ethoxide, afforded 3-(1-methyl-6-pyrazolo[5,4-*b*]pyridyl)tropolones **11a,b** in good yields (**11a**, 73%; **11b**, 72%).

tion, it is known that the compound **20** is a tautomer of 2-acetylbenzoic acid (**17**) [10]. This tautomerism predominates to the phthalide **20**, exclusively. Thus, commercially available "2-acetylbenzoic acid" (**17**), which is a minor tautomeric form, was treated with **2** to give 2-(1,8-naphthyridin-2-yl)benzoic acid (**21**) in 28% yield. On the other hand, 7-acetyl-2-methoxytropone (**13**) reacted with **2** to afford a rearranged product **21** in 54% yield. This reaction was carried out in the presence of potassium hydroxide to give 3-(1,8-naphthyridin-2-yl)tropolone (**3a**) and 3-acetyltropolone (**1a**) in low yields (**3a**, 34%; **1a**, 28%). 3- and 7-Acetyl-2-aminotropone **14** and **15** reacted with **2** at room temperature by catalysis of sodium ethoxide to give respectively 2-amino-3- and -7-(1,8-naph-

Table 2

Reactivities of Aminoheteroarenecarbaldehydes in the Reactions with 3-Acetyltropolone (**1a**) [a]

High ← Reactivity → Low

	 **6**	 **5**	 **4**	 **2**	 [b]	 **7**
Temp (°C)	RT	65	65	65	65	65
Time (h)	24	14	17	24	24	24
Product (Yield/%)	91	90	88	96	24	6
1a (Recv/%)	3	4	5	2	68	84

[a] Molar ratio, **1a**:aldehyde:potassium hydroxide = 1:1:2. [b] Ref 9.

These results of the reactions of **1a** with a series of aminopyridinecarbaldehydes and related compounds in the presence of potassium hydroxide in 50% methanol are summarized in Table 2 and revealed that the reactivities of the aldehydes decreased in the following order: 3-amino-2-pyrazinecarbaldehyde (**6**) > 3-amino-4-pyridinecarbaldehyde (**5**) > 4-amino-3-pyridinecarbaldehyde (**4**) > 2-amino-3-pyridinecarbaldehyde (**2**) > 2-aminobenzaldehyde > 5-amino-1-methyl-4-pyrazolecarbaldehyde (**7**). This order might be due to electron-deficiency and electron-enrichment of these heterocyclic ring systems, as described above.

Reactions of 3-Acetyltropolone Derivatives and Related Compounds with 2-Amino-3-pyridinecarbaldehyde (**2**).

A methanolic solution of 3-acetyl-2-methoxytropone (**12**) and 2-amino-3-pyridinecarbaldehyde (**2**) was heated at 60° in the presence of sodium methoxide to afford 3-hydroxy-3-methylphthalide (**20**) in 54% yield. This reaction indicates that the tropone **12** itself cyclized to the phthalide **20** *via* a base-catalyzed rearrangement. In addi-

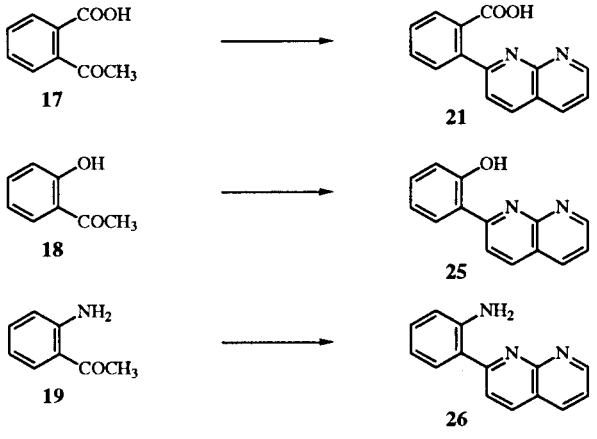
thyrdin-2-yl)tropones **22** and **23** in good yields (**22**, 89%; **23**, 70%). In the same way, the reaction of 7-acetyl-2-methylaminotropone (**16**) afforded 2-methylamino-7-(1,8-naphthyridin-2-yl)tropone (**24a**) in 66% yield. However, the reaction in the presence of potassium hydroxide in 50% aqueous methanol produced partial hydrolysis and gave **24a** (36%) and **3a** (46%).

In the connection with the troponoid substrates, the reactions of acetyl-substituted phenol **18** and aniline **19** with 2-amino-3-pyridinecarbaldehyde (**2**) were also carried out in the presence of potassium hydroxide in 50% methanol yielded the corresponding 2-(1,8-naphthyridin-2-yl)phenol (**25**) [11] and 2-(1,8-naphthyridin-2-yl)aniline (**26**) in 98 and 88% yield, respectively.

Physical and Chemical Properties of 3-(1,8-Naphthyridin-2-yl)tropolones **3a-e** and Related Compounds.

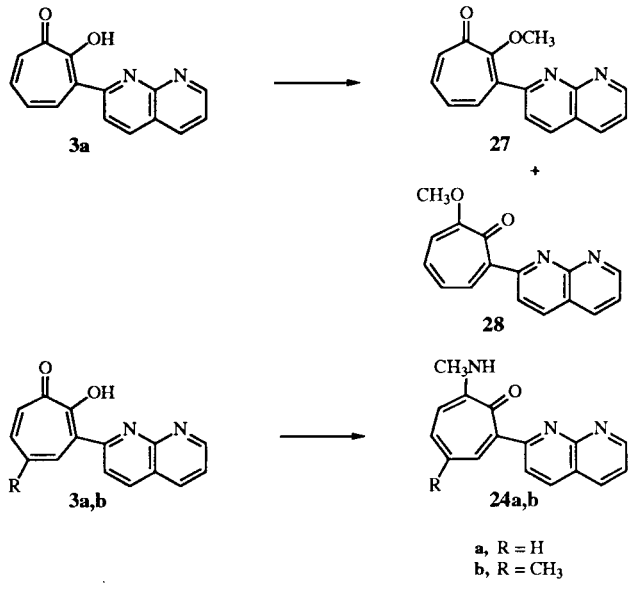
Variously heterocyclic substituted tropolones were prepared as stable compounds in high yields. Their ir spectra show typical ν_{OH} and $\nu_{C=O}$ absorption bands for

Scheme 3



tropolones. The ^1H and ^{13}C nmr spectra also gave satisfactory values. In the uv spectra of 3-(1,8-naphthyridin-2-yl)tropolone (**3a**), five absorption bands were observed at 214, 251, 313, 343, and 375 nm. The last two bands were shifted to longer wavelengths than those of tropolone and 1,8-naphthyridine. This phenomenone was also observed in the other products and suggested a π-π conjugation between the two ring systems, tropolone and naphthyridine.

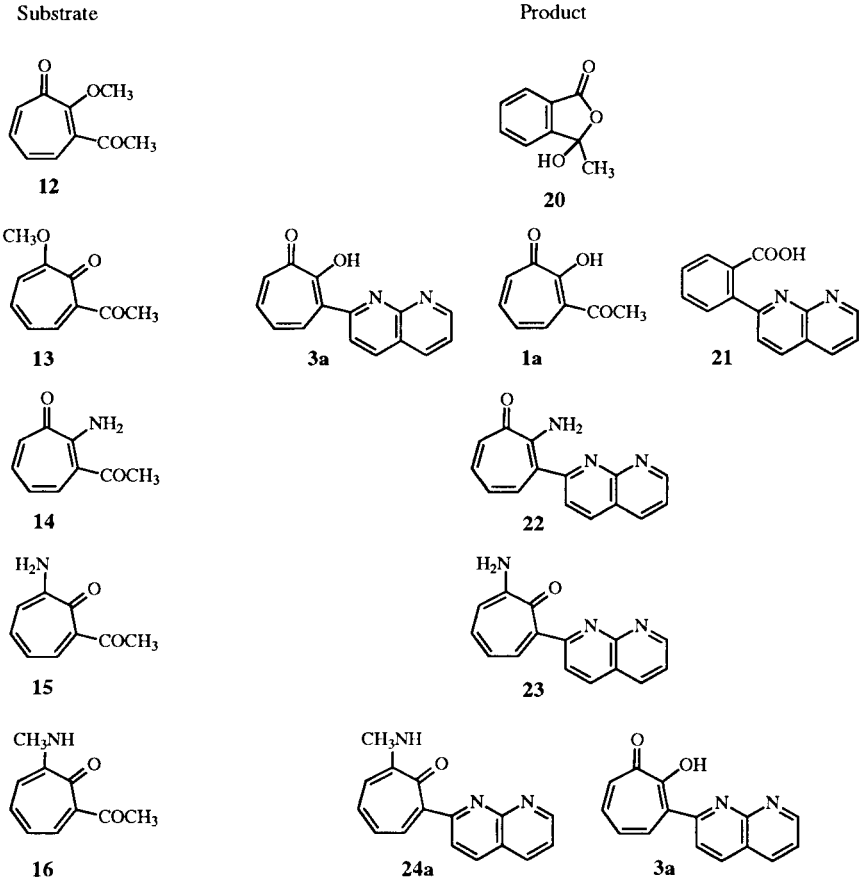
Scheme 4



When 3-(1,8-naphthyridin-2-yl)tropolone (**3a**) was treated with a diazomethane solution, two isomeric 2-methoxy-3- and -7-(1,8-naphthyridin-2-yl)tropone **27** and

Table 3

Reactions of 3-Acetyltropolone Derivatives with 2-Amino-3-pyridinecarbaldehyde (**2**)



28 were obtained in 38 and 50% yield, respectively. Consequently, it was confirmed that a tautomeric equilibrium exists in compound **3a** as well as in other tropolones.

Furthermore, when compound **3a** was allowed to stand in 40% aqueous methylamine solution it afforded exclusively 2-methylamino-7-(1,8-naphthyridin-2-yl)tropone (**24a**) in 83% yield as well as amination of other 3-acetyltropolones [10]. Similarly, compound **3b** gave 5-methyl-2-methylamino-7-(1,8-naphthyridin-2-yl)tropone (**24b**) in 90% yield. These results indicate that the tropolone nucleus of the naphthyridinyl-substituted tropolones **3a,b** are unusually activated for nucleophilic attack of methylamine by the electron-deficient six-membered heterocyclic ring. In addition, compound **24a** was hydrolyzed in a potassium hydroxide solution to afford tropolone **3a** in 86% yield.

EXPERIMENTAL

Measurements.

All melting points were determined with a Yanagimoto MP S-2 apparatus and are uncorrected. The ir spectra were taken on a JASCO A-102 spectrophotometer and the uv spectra on a Hitachi U-3210 spectrophotometer. The nmr spectra were recorded with a JEOL JNM-EX 90 spectrometer (90 MHz for ^1H and 22.5 MHz for ^{13}C) and partly with a JEOL JNM-A500 spectrometer (500 MHz). The mass spectra were measured on a JEOL JMS-01-SG spectrometer.

Materials.

Unless otherwise stated, chemicals were purchased and were used without further purification. The following materials were prepared according to literature procedures: 3-acetyltropolones **1a** [12], **1b** [13], **1c** [13], **1d** [13], **1e** [14], methoxy- and amino-substituted tropones **12** [12], **13** [12], **14** [15], **15** [15], **16** [15], amino-substituted pyridinecarbaldehydes **2** [16], **4** [17], **5** [17], 3-aminopyrazine-2-carbaldehyde (**6**) [18] and 5-amino-1-methyl-4-pyrazolecarbaldehyde (**7**) [19].

3-(1,8-Naphthyridin-2-yl)tropolone (**3a**).

The reactions of 3-acetyltropolone (**1a**) (164 mg, 1.0 mmole) with 2-amino-3-pyridinecarbaldehyde (**2**) (122-183 mg, 1.0-1.5 mmoles) were carried out in an appropriate solvent (8 ml) under the conditions listed in Table 1. The reaction mixture was quenched with iced-water, acidified slightly with 2*M* hydrochloric acid, and extracted with chloroform (3 x 30 ml). After drying over sodium sulfate, the concentrated residue was purified on a column containing Wakogel C-200 (10 g) with chloroform-methanol (50:1) as an eluent to afford 3-(1,8-naphthyridin-2-yl)tropolone (**3a**) as yellow needles (from methanol) in yields shown in Table 1. In some cases, the starting material **1a** was recovered. Compound **3a** had mp 204.5-205.5°; ir (potassium bromide): ν max 3325 (OH), 1603 cm^{-1} (C=O); uv (methanol): λ max 214 (log ε 4.37), 251 (4.37), 313 (3.99), 343 (3.95), 375 nm (3.97); ^1H nmr (deuteriochloroform, 500 MHz): δ 7.22 (1H, dd, J = 10.37, 9.15 Hz, 5-H), 7.45 (1H, dd, J = 10.37, 9.15 Hz, 6-H), 7.46 (1H, d, J = 10.37 Hz, 7-H), 7.51 (1H, dd, J = 8.54, 4.27 Hz, 6'-H), 8.20 (1H, d, J = 8.54 Hz, 4'-H), 8.23 (1H, dd, J = 8.54, 2.44 Hz, 5'-H), 8.23 (1H, d, J = 8.54 Hz, 3'-H), 8.47 (1H, d, J = 10.37 Hz, 4-H), 9.13 (1H, dd, J = 4.27, 2.44 Hz, 7'-H); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 120.6 (=CH-), 121.7 (=C<), 122.5 (=CH-), 124.0 (=CH-), 127.1 (=CH-), 136.6 (=CH-), 137.2 (=CH-), 137.6 (=C<), 137.9 (=CH-), 140.4 (=CH-), 153.5 (=CH-), 155.4 (=C<), 161.3 (=C<), 170.2 (=C<), 172.8 (=C<); ms: m/z (%) 250 (M^+, 39), 222 (100), 194 (41), 168 (45).

Anal. Calcd. for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.03; N, 11.19. Found: C, 72.08; H, 4.02; N, 11.37.

5-Methyl-3-(1,8-naphthyridin-2-yl)tropolone (**3b**).

To a solution of 3-acetyl-5-methyltropolone (**1b**) (178 mg, 1.0 mmole) and 2 (183 mg, 1.5 mmoles) in methanol (4 ml) was added a solution of potassium hydroxide (112 mg, 2.0 mmoles) in water (4 ml). The mixture was stirred for 24 hours at 65° and worked up as described above to give 5-methyl-3-(1,8-naphthyridin-2-yl)tropolone (**3b**) in a yield of 230 mg (87%) as yellow needles (from methanol), mp 188.5-189.5°; ir (potassium bromide): ν max 3450 (OH), 1605 cm^{-1} (C=O); uv (methanol): λ max 214 (log ε 4.39), 252 (4.39), 317 (4.03), 344 (3.93), 383 nm (3.96); ^1H nmr (deuteriochloroform): δ 2.53 (3H, s, CH_3), 7.34 (2H, m, 6-,7-H), 7.51 (1H, dd, J = 8.06, 4.25 Hz, 6'-H), 8.11 (1H, d, J = 8.50 Hz, 4'-H), 8.20 (1H, s, 4-H), 8.23 (1H, dd, J = 8.06, 1.90 Hz, 5'-H), 8.24 (1H, d, J = 8.50 Hz, 3'-H), 9.14 (1H, dd, J = 4.25, 1.90 Hz, 7'-H); ^{13}C nmr (deuteriochloroform): δ 26.4 (CH_3), 120.6 (=CH-), 122.2 (=C<), 122.4 (=CH-), 124.6 (=CH-), 136.2 (=CH-), 136.6 (=C<), 136.8 (=CH-), 138.5 (=C<), 138.6 (=CH-), 143.9 (=CH-), 153.6 (=CH-), 156.1 (=C<), 161.1 (=C<), 169.1 (=C<), 171.5 (=C<); ms: m/z (%) 264 (M^+, 71), 236 (100), 207 (77), 181 (13).

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.63; H, 4.54; N, 10.56.

7-Bromo-5-methyl-3-(1,8-naphthyridin-2-yl)tropolone (**3c**).

The reaction of 3-acetyl-7-bromo-5-methyltropolone (**1c**) (257 mg, 1.0 mmole) with **2** (183 mg, 1.5 mmoles) was carried out and worked up as described above to give 7-bromo-5-methyl-3-(1,8-naphthyridin-2-yl)tropolone (**3c**) in a yield of 298 mg (87%) as yellow needles (from methanol), mp 199-200°; ir (potassium bromide): ν max 3455 (OH), 1607 cm^{-1} (C=O); uv (methanol): λ max 210 (log ε 4.44), 263 (4.42), 314 (4.09), 391 nm (3.93); ^1H nmr (deuteriochloroform): δ 2.53 (3H, s, CH_3), 7.57 (1H, dd, J = 8.20, 4.25 Hz, 6'-H), 8.01-8.31 (3H, m), 8.07 (1H, d, J = 8.50 Hz, 4'-H), 8.26 (1H, d, J = 8.50 Hz, 3'-H), 9.17 (1H, dd, J = 4.25, 1.90 Hz, 7'-H); ^{13}C nmr (deuteriochloroform): δ 26.4 (CH_3), 122.3 (=C<), 122.6 (=CH-), 124.5 (=CH-), 124.8 (=C<), 134.0 (=C<), 136.1 (=C<), 136.5 (=CH-), 136.9 (=CH-), 142.8 (=CH-), 143.8 (=CH-), 153.8 (=CH-), 156.0 (=C<), 160.2 (=C<), 165.8 (=C<), 167.9 (=C<); ms: m/z (%) 342/344 (M^+, 41/40), 314 (65), 299 (2), 285 (12), 263 (100), 235 (47), 207 (95).

Anal. Calcd. for $C_{16}H_{11}BrN_2O_2$: M_r^+, 342.0005/343.9985. Found: M_r^+, 342.0009/343.9959.

5-Isopropyl-3-(1,8-naphthyridin-2-yl)tropolone (**3d**).

The reaction of 3-acetyl-5-isopropyltropolone (**1d**) (206 mg, 1.0 mmole) with **2** (183 mg, 1.5 mmoles) was carried out and worked up as described above to give 5-isopropyl-3-(1,8-naphthyridin-2-yl)tropolone (**3d**) in a yield of 266 mg (91%) as yellow needles (from methanol), mp 181-182°; ir (potassium bromide): ν max 3100 (OH), 1601 cm^{-1} (C=O); uv (methanol): λ max 213 (log ε 4.43), 252 (4.38), 312 (4.03), 344 (3.93), 378 nm (3.92); ^1H nmr (deuteriochloroform): δ 1.30 (6H, d, J = 6.89 Hz,

2 x CH_3), 3.03 (1H, sept, J = 6.89 Hz, 5-CH), 7.42 (2H, m, 6-,7-H), 7.52 (1H, dd, J = 8.10, 4.21 Hz, 6'-H), 8.10 (1H, d, J = 8.50 Hz, 4'-H), 8.20 (1H, s, 4-H), 8.23 (1H, dd, J = 8.10, 1.95 Hz, 5'-H), 8.25 (1H, d, J = 8.50 Hz, 3'-H), 9.15 (1H, dd, J = 4.21, 1.95 Hz, 7'-H); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 23.5 (2 x CH_3), 37.2 (5-CH), 121.4 (=CH-), 121.8 (=C<), 122.6 (=CH-), 124.3 (=CH-), 135.5 (=CH-), 136.6 (=CH-), 137.3 (=CH-), 137.6 (=C<), 139.7 (=CH-), 147.4 (=C<), 153.5 (=CH-), 155.4 (=C<), 161.8 (=C<), 169.1 (=C<), 171.5 (=C<); ms: m/z (%) 292 (M^+, 36), 277 (19), 264 (20), 249 (100), 221 (13).

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 9.58; M_r^+, 292.1212. Found: C, 73.88; H, 5.60; N, 9.66; M_r^+, 292.1201.

5-Bromo-3-(1,8-naphthyridin-2-yl)tropolone (**3e**).

The reaction of 3-acetyl-5-bromotropolone (**1e**) (243 mg, 1.0 mmole) with **2** (183 mg, 1.5 mmoles) was carried out and worked up as described above to give 5-bromo-3-(1,8-naphthyridin-2-yl)tropolone (**3e**) in a yield of 316 mg (96%) as greenish yellow plates (from ethanol-acetic acid), mp 238-239°; ir (potassium bromide): ν max 3449 (OH), 1601 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 7.14 (1H, d, J = 11.13 Hz, 7-H), 7.69 (1H, dd, J = 8.21, 4.25 Hz, 6'-H), 7.84 (1H, dd, J = 11.13, 2.20 Hz, 6-H), 8.00 (1H, d, J = 8.50 Hz, 4'-H), 8.24 (1H, d, J = 2.20 Hz, 4-H), 8.52 (1H, d, J = 8.50 Hz, 3'-H), 8.55 (1H, dd, J = 8.21, 1.91 Hz, 5'-H), 9.12 (1H, dd, J = 4.25, 1.91 Hz, 7'-H).

Anal. Calcd. for $C_{15}H_9BrN_2O_2$: C, 54.74; H, 2.76; N, 8.51. Found: C, 54.83; H, 2.82; N, 8.49.

3-(1,6-Naphthyridin-2-yl)tropolone (**8a**).

A mixture of **1a** (164 mg, 1.0 mmole) and 4-amino-3-pyridinecarbaldehyde (**4**) (122 mg, 1.0 mmole) in 50% aqueous methanol (8 ml) was stirred for 17 hours at 65° in the presence of potassium hydroxide (112 mg, 2.0 mmoles) and worked up as described above to give 3-(1,6-naphthyridin-2-yl)tropolone (**8a**) in a yield of 220 mg (88%) as yellow needles (from methanol-chloroform), mp 268-269°; ir (potassium bromide): ν max 3560 (OH), 1610 cm^{-1} (C=O); uv (methanol): λ max 226 (log ε 4.37), 250 (4.33), 320 (3.90), 376 (3.84), 414 (3.71), 444 nm (3.45); ^1H nmr (deuteriodimethyl sulfoxide): δ 7.10-7.67 (3H, m, 5-,6-,7-H), 7.93- 8.03 (1H, m, 4-H), 7.96 (1H, d, J = 6.00 Hz, 8'-H), 8.00 (1H, d, J = 8.61 Hz, 4'-H), 8.58 (1H, dd, J = 8.61, 0.88 Hz, 3'-H), 8.77 (1H, d, J = 6.00 Hz, 7'-H), 9.43 (1H, d, J = 0.88 Hz, 5'-H); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 120.4 (=CH-), 121.4 (=C<), 122.4 (=CH-), 124.7 (=CH-), 127.1 (=CH-), 134.9 (=CH-), 137.8 (=C<), 138.1 (=CH-), 140.3 (=CH-), 146.7 (=CH-), 149.6 (=C<), 152.8 (=CH-), 163.1 (=C<), 170.0 (=C<), 172.9 (=C<).

Anal. Calcd. for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.03; N, 11.19. Found: C, 72.13; H, 3.97; N, 11.15.

5-Methyl-3-(1,6-naphthyridin-2-yl)tropolone (**8b**).

The reaction of **1b** (178 mg, 1.0 mmole) and **4** (122 mg, 1.0 mmole) was carried out and worked up as described above to give 5-methyl-3-(1,6-naphthyridin-2-yl)tropolone (**8b**) in a yield of 238 mg (90%) as yellow needles (from methanol), mp 233-234°; ir (potassium bromide): ν max 3440 (OH), 1612 cm^{-1} (C=O); uv (methanol): λ max 216 (log ε 4.38), 231 (4.40), 245 (4.41), 318 (3.93), 382 nm (3.94); ^1H nmr (deuteriochloroform): δ 2.52 (3H, s, CH_3), 7.35 (2H, s, 6-,7-H), 7.94 (1H, d, J = 6.01 Hz, 8'-H), 7.98 (1H, s, 4-H), 8.02 (1H, d, J = 8.65 Hz, 4'-H), 8.32 (1H, dd, J = 8.65, 0.88 Hz, 3'-H), 8.79 (1H, d, J = 6.01 Hz, 7'-H), 9.31 (1H, d, J = 0.88 Hz, 5'-H); ^{13}C nmr (deuteriochloroform): δ 26.4 (CH_3), 120.9 (=CH-), 122.1 (=CH-), 122.9 (=C<), 124.8 (=CH-), 134.9 (=CH-), 136.8 (=C<), 138.5 (=C<), 138.7 (=CH-), 142.9 (=CH-), 147.1 (=CH-), 150.4 (=C<), 152.6 (=CH-), 162.7 (=C<), 169.3 (=C<), 171.3 (=C<).

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 73.03; H, 4.64; N, 10.69.

3-(1,7-Naphthyridin-2-yl)tropolone (**9a**).

The reaction of **1a** (164 mg, 1.0 mmole) with 3-amino-4-pyridinecarbaldehyde (**5**) (122 mg, 1.0 mmole) in 50% aqueous methanol (8 ml) was stirred for 14 hours at 65° in the presence of potassium hydroxide (112 mg, 2.0 mmoles) and worked up as described above to give 3-(1,7-naphthyridin-2-yl)tropolone (**9a**) in a yield of 225 mg (90%) as yellow needles (from methanol), mp 225-226°; ir (potasium bromide): ν max 3460 (OH), 1600 cm^{-1} (C=O); uv (methanol): λ max 213 (log ε 4.39), 254 (4.41), 336 (3.89), 374 nm (3.89); ^1H nmr (deuteriochloroform): δ 7.13-7.43 (4H, m, 4-,5-,6-,7-H), 7.70 (1H, dd, J = 5.57, 1.03 Hz, 5'-H), 8.20 (2H, s, 3'-,4'-H), 8.66 (1H, d, J = 5.57 Hz, 6'-H), 9.56 (1H, s, 8'-H); ^{13}C nmr (deuteriochloroform): δ 119.7 (=CH-), 120.7 (=CH-), 127.3 (=CH-), 127.9 (=CH-), 130.5 (=C<), 133.9 (=CH-), 137.1 (=C<), 138.5 (=CH-), 141.7 (=CH-), 143.4 (=C<), 144.2 (=CH-), 154.3 (=CH-), 159.4 (=C<), 170.5 (=C<), 172.5 (=C<).

Anal. Calcd. for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.03; N, 11.19. Found: C, 71.76; H, 3.91; N, 11.22.

5-Methyl-3-(1,7-naphthyridin-2-yl)tropolone (**9b**).

The reaction of **1b** (178 mg, 1.0 mmole) with **5** (122 mg, 1.0 mmole) was carried out and worked up as described above to give 5-methyl-3-(1,7-naphthyridin-2-yl)tropolone (**9b**) in a yield of 243 mg (92%) as yellow crystals (from methanol), mp 210-210.5°; ir (potassium bromide): ν max 3050 (OH), 1616 cm^{-1} (C=O); uv (methanol): λ max 214 (log ε 4.40), 232 (4.40), 254 (4.43), 340 (3.90), 381 nm (3.91); ^1H nmr (deuteriochloroform): δ 2.54 (3H, s, CH_3), 7.36 (2H, s, 6-,7-H), 7.69 (1H, d, J = 5.57 Hz, 5'-H), 8.05 (1H, s, 4-H), 8.15 (2H, s, 3'-,4'-H), 8.65 (1H, d, J = 5.57 Hz, 6'-H), 9.57 (1H, s, 8'-H); ^{13}C nmr (deuteriochloroform): δ 26.4 (CH_3), 119.7 (=CH-), 120.8 (=CH-), 127.4 (=CH-), 130.5 (=C<), 133.8 (=CH-), 136.8 (=C<), 138.5 (=C<), 138.6 (=CH-), 143.0 (=CH-), 143.3 (=C<), 144.1 (=CH-), 154.2 (=CH-), 159.8 (=C<), 169.2 (=C<), 171.5 (=C<).

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.49; H, 4.69; N, 10.58.

3-(6-Pyrido[2,3-*b*] pyrazinyl)tropolone (**10a**).

To a solution of **1a** (164 mg, 1.0 mmole) and 3-amino-2-pyrazinecarbaldehyde (**6**) (135 mg, 1.0 mmole) in methanol (4 ml) was added a solution of potassium hydroxide (112 mg, 2.0 mmoles) in water (4 ml). The mixture was stirred for 24 hours at room temperature and worked up as described above to give 3-(6-pyrido[2,3-*b*]pyrazinyl)tropolone (**10a**) in a yield of 228 mg (91%) as yellow needles (from methanol-chloroform), mp 275-276°; ir (potassium bromide): ν max 3430 (OH), 1600 cm^{-1} (C=O); uv (methanol): λ max 211 (log ε 4.33), 247 (4.35), 315 (4.05), 344 (3.95), 379 nm (4.00); ^1H nmr (deuteriodimethyl sulfoxide): δ 7.15-7.59 (3H, m, 5-,6-,7-H), 8.07 (1H, dd, J = 9.26, 0.95 Hz, 4-H), 8.23 (1H, d, J = 8.64 Hz, 4'-H), 8.58 (1H, d, J = 8.64 Hz, 3'-H), 9.08 (1H, d, J = 1.90 Hz, 6'- or 7'-H), 9.16 (1H, d, J = 1.90 Hz, 6'- or 7'-H); ms: m/z (%) 251 (M^+, 47), 223 (100), 195 (37), 169 (43).

Anal. Calcd. for $C_{14}H_9N_3O_2$: M_r^+, 251.0696. Found: M_r^+, 251.0690.

5-Methyl-3-(6-pyrido[2,3-*b*]pyrazinyl)tropolone (**10b**).

The reaction of **1b** (178 mg, 1.0 mmole) and **6** (135 mg, 1.0 mmole) was carried out under stirring for 26 hours and worked up as described above to give 5-methyl-3-(6-pyrido[2,3-*b*]-pyrazinyl)tropolone (**10b**) in a yield of 239 mg (90%) as yellow needles (from methanol-chloroform), mp 246-247°; ir (potassium bromide): ν max 3460 (OH), 1602 cm^{-1} (C=O); uv (methanol): λ max 211 (log ε 4.34), 248 (4.35), 317 (4.11), 346 (3.92), 385 nm (3.96); ^1H nmr (deuteriodimethyl sulfoxide): δ 2.52 (3H, s, CH_3), 7.36 (2H, s, 6-,7-H), 8.12 (1H, s, 4-H), 8.29 (1H, d, J = 8.72 Hz, 4'-H), 8.50 (1H, d, J = 8.72 Hz, 3'-H), 9.02 (1H, d, J = 1.76 Hz, 6'- or 7'-H), 9.10 (1H, d, J = 1.76 Hz, 6'- or 7'-H); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 26.1 (CH_3), 120.2 (=CH-), 128.0 (=CH-), 136.7 (=C<), 137.2 (=CH-), 137.7 (=C<), 137.8 (=C<), 138.3 (=CH-), 143.2 (=CH-), 146.3 (=CH-), 147.7 (=CH-), 150.9 (=C<), 162.2 (=C<), 168.7 (=C<), 172.0 (=C<); ms: m/z (%) 265 (M^+, 71), 250 (3), 237 (100), 222 (11), 208 (73), 194 (7).

Anal. Calcd. for $C_{15}H_{11}N_3O_2$: M^+, 265.0852. Found: M^+, 265.0865.

5-Isopropyl 3-(6-pyrido[2,3-*b*]pyrazinyl)tropolone (**10d**).

The reaction of **1d** (206 mg, 1.0 mmole) and **6** (135 mg, 1.0 mmole) was carried out under stirring for 24 hours and worked up as described above to give 5-isopropyl-3-(6-pyrido[2,3-*b*]-pyrazinyl)tropolone (**10d**) in a yield of 217 mg (74%) as yellow needles (from methanol), mp 168.5-169.5°; ir (potassium bromide): ν max 3430 (OH), 1602 cm^{-1} (C=O); uv (methanol): λ max 216 (log ε 4.30), 246 (4.33), 317 (4.14), 346 (3.96), 383 nm (3.99); ^1H nmr (deuteriochloroform): δ 1.31 (6H, d, J = 6.88 Hz, 2 x CH_3), 3.03 (1H, sept, J = 6.88 Hz, 5-CH), 7.40 (2H, s, 6-,7-H), 8.24 (1H, s, 4-H), 8.33 (1H, d, J = 8.79 Hz, 4'-H), 8.52 (1H, d, J = 8.79 Hz, 3'-H), 8.98 (1H, d, J = 1.76 Hz, 6'- or 7'-H), 9.09 (1H, d, J = 1.76 Hz, 6'- or 7'-H); ^{13}C nmr (deuteriochloroform): δ 23.9 (2 x CH_3), 38.4 (5-CH), 121.1 (=CH-), 128.1 (=CH-), 136.3 (=CH-), 136.6 (=C<), 137.6 (=CH-), 138.1 (=C<), 142.2 (=CH-), 146.1 (=CH-), 147.7 (=CH-), 149.2 (=C<), 151.3 (=C<), 162.4 (=C<), 169.2 (=C<), 171.4 (=C<); ms: m/z (%) 293 (M^+, 34), 278 (16), 265 (18), 250 (100).

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33; M_r^+, 293.1165. Found: C, 69.73; H, 5.24; N, 14.52; M_r^+, 293.1163.

3-(1-Methyl-6-pyrazolo[5,4-*b*]pyridyl)tropolone (**11a**).

To a solution of **1a** (164 mg, 1.0 mmole) and 5-amino-1-methyl-4-pyrazolecarbaldehyde (**7**) (138 mg, 1.1 mmoles) in absolute ethanol (2 ml) was added a sodium ethoxide solution, prepared from sodium (46 mg, 2.0 mmoles) and absolute ethanol (2 ml). The mixture was heated for 1 hour under refluxing and worked up as described above to give 3-(1-methyl-6-pyrazolo[5,4-*b*]pyridyl)tropolone (**11a**) in a yield of 185 mg (73%) as yellow needles (from methanol-chloroform), mp 211-212°; ir (potassium bromide): ν max 3450 (OH), 1600 cm^{-1} (C=O); uv (methanol): λ max 214 (log ε 4.36), 244 (4.25), 277 (4.09), 318 (3.99), 375 nm (3.91); ^1H nmr (deuteriochloroform): δ 4.19 (3H, s, CH_3), 7.12-7.51 (3H, m, 5-,6-,7-H), 7.70 (1H, d, J = 8.50 Hz, 4'-H), 8.04 (1H, s, 5'-H), 8.11 (1H, d, J = 8.50 Hz, 3'-H), 8.05-8.20 (1H, m, 4-H); ^{13}C nmr (deuteriochloroform): δ 34.0 (CH_3), 114.6 (=C<), 118.7 (=CH-), 121.5 (=CH-), 127.5 (=CH-), 129.5 (=CH-), 131.7 (=CH-), 137.1 (=C<), 138.1 (=CH-), 141.5 (=CH-), 150.4 (=C<), 156.1 (=C<), 171.2 (=C<), 171.6 (=C<).

Anal. Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.21; H, 4.33; N, 16.39.

5-Methyl-3-(1-methyl-6-pyrazolo[5,4-*b*]pyridyl)tropolone (**11b**).

The reaction of **1b** (178 mg, 1.0 mmole) and **7** (138 mg, 1.1 mmoles) was carried out and worked up as described above to give 5-methyl-3-(1-methyl-6-pyrazolo[5,4-*b*]pyridyl)tropolone (**11b**) in a yield of 192 mg (72%) as yellow needles (from methanol), mp 210-211°; ir (potassium bromide): ν max 3450 (OH), 1600 cm^{-1} (C=O); uv (methanol): λ max 214 (log ε 4.34), 248 (4.26), 276 (4.11), 318 (4.00), 378 nm (3.91); ^1H nmr (deuteriochloroform): δ 2.52 (3H, s, 5-CH_3), 4.20 (3H, s, N-CH_3), 7.35 (2H, s, 6-,7-H), 7.62 (1H, d, J = 8.35 Hz, 4'-H), 7.92 (1H, s, 4-H), 8.04 (1H, s, 5'-H), 8.10 (1H, d, J = 8.35 Hz, 3'-H); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 25.4 (5-CH_3), 33.6 (N-CH_3), 113.8 (=C<), 118.5 (=CH-), 121.2 (=CH-), 129.6 (=CH-), 131.7 (=CH-), 137.0 (=CH- + =C<), 137.5 (=C<), 141.2 (=CH-), 149.7 (=C<), 157.2 (=C<), 169.0 (=C<), 170.9 (-C<).

Anal. Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.41; H, 4.90; N, 15.72. Found: C, 67.58; H, 4.95; N,15.52.

3-Hydroxy-3-methylphthalide (**20**).

To a solution of 3-acetyl-2-methoxytropone (**12**) (178 mg, 1.0 mmole) and **2** (134 mg, 1.1 mmoles) in absolute ethanol (4 ml) was added a sodium ethoxide solution, prepared from sodium (46 mg, 2.0 mmoles) and absolute ethanol (2 ml). The mixture was heated for 6 hours at 60° and worked up as described above to give 3-hydroxy-3-methylphthalide (**20**) in a yield of 115 mg (70%) as colorless crystals (from benzene-hexane), mp 119.5-120.5° (lit [10a], 117.5-119.5°); ir (chloroform): ν max 3320 (OH), 1770 cm^{-1} (C=O); uv (methanol): λ max 206 (log ε 4.05), 229 (3.97), 276 (3.17), 282 nm (3.14); ^1H nmr (deuteriochloroform): δ 1.97 (3H, s, CH_3), 4.83 (1H, s, OH), 7.50-7.87 (4H, m); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 27.4 (CH_3), 79.1 (3-C), 123.6 (=CH-), 126.0 (=CH-), 127.3 (=C<), 130.0 (=CH-), 133.6 (=CH-), 148.6 (=C<), 167.9 (1-C=O).

Anal. Calcd. for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 65.77; H, 4.86.

2-(1,8-Naphthyridin-2-yl)benzoic Acid (**21**).

a) To a solution of 7-acetyl-2-methoxytropone (**13**) (178 mg, 1.0 mmole) and **2** (134 mg, 1.1 mmoles) in absolute ethanol (4 ml) was added a sodium ethoxide solution, prepared from sodium (46 mg, 2.0 mmoles) and absolute ethanol (2 ml). The mixed solution was refluxed for 1 hour. The reaction mixture was quenched with iced-water and extracted with chloroform (3 x 30 ml). The aqueous layer was acidified with 2*M* hydrochloric acid and extracted with chloroforom (3 x 30 ml). The extract was dried over sodium sulfate and evaporated to give 2-(1,8-naphthyridin-2-yl)benzoic acid (**21**) in a yield of 135 mg (54%) as pale yellow crystals (from benzene-methanol), mp 180-181°; ir (potassium bromide): ν max 3050 (COOH), 1691 cm^{-1} (C=O); uv (methanol): λ max 220 (log ε 4.43), 315 nm (4.01); ^1H nmr (deuteriodimethyl sulfoxide): δ 7.55-7.94 (4H, m), 7.68 (1H, dd, J = 8.06, 4.10 Hz, 6'-H), 7.79 (1H, d, J = 8.50 Hz, 4'-H), 8.50 (1H, d, J = 8.50 Hz, 3'-H), 8.51 (1H, dd, J = 8.06, 2.05 Hz, 5'-H), 9.10 (1H, dd, J = 4.10, 2.05 Hz, 7'-H); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 121.2 (=C<), 122.1 (=CH-), 122.5 (=CH-), 128.7 (=CH-), 129.3 (=CH-), 130.2 (=CH-), 130.9 (=CH-), 132.4 (=C<), 137.2 (=CH-), 137.4 (=C<), 140.3

(=C<), 153.5 (=CH-), 154.9 (=CH-), 161.8 (=C<), 168.8 (=C<); ms: m/z (%) 250 (M^+, 0.5), 206 (100).

Anal. Calcd. for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.03; N, 11.20; M_r^+, 250.0743. Found: C,71.72; H, 3.79; N, 10.92; M_r^+, 250.0745.

b) A mixture of **13** (178 mg, 1.0 mmole) and **2** (134 mg, 1.1 mmoles) in water (4 ml) was stirred for 24 hours at 65° in the presence of potassium hydroxide (112 mg, 2.0 mmoles). The reaction mixture was quenched with iced-water and extracted with chloroform (3 x 30 ml). The chloroform extract gave **2** (90 mg, 49%) after drying over sodium sulfate and evaporation. The aqueous layer was acidified with 2*M* hydrochloric acid and extracted with chloroform (3 x 30 ml). After drying over sodium sulfate, the concentrated residue was chromatographed on a column containing Wakogel C-200 (10 g) with chloroform-methanol (50:1) as eluent to give **3a** (85 mg, 34%) and **1a** (46 mg, 28%).

c) A mixture of 2-acetylbenzoic acid (**17**) (165 mg, 1.0 mmole) and **2** (183 mg, 1.5 mmoles) in 50% aqueous methanol (6 ml) was stirred for 25.5 hours at 65° in the presence of potassium hydroxide (112 mg, 2.0 mmoles). After acidifying with 2*M* hydrochloric acid, the chloroform extract was evaporated to dryness. The resulting solid was recrystallized from benzene-methanol to give **21** in a yield of 70 mg (28%).

2-Amino-3-(1,8-naphthyridin-2-yl)tropone (**22**).

To a solution of 3-acetyl-2-aminotropone (**14**) (163 mg, 1.0 mmole) and **2** (134 mg, 1.1 mmoles) in absolute ethanol (4 ml) was added a sodium ethoxide solution, prepared from sodium (46 mg, 2.0 mmoles) and absolute ethanol (2 ml). The mixture was stirred for 2 hours at room temperature to precipitate a small amount of 2-amino-3-(1,8-naphthylidin-2-yl)tropone (**22**). The filtrate was quenched with water and extracted with chloroform (3 x 30 ml). The extract was dried over sodium sulfate and concentrated. The residue was chromatographed on a Wakogel B-10 plate (30 x 30 cm) with ethyl acetate-methanol (10:1) to give a major part of **22** in a combined yield of 222 mg (89%) as orange plates (from methanol), mp 189-190°; ir (potassium bromide): ν max 3335 (NH), 3050 (NH), 1600 cm^{-1} (C=O); uv (methanol): λ max 215 (log ε 4.43), 236 (4.38), 311 (4.14), 321 (4.11), 423 nm (4.08); ^1H nmr (deuteriochloroform): δ 6.56-6.80 (1H, m, 5-H), 7.09-7.32 (2H, m, 6-,7-H), 7.51 (1H, dd, J = 8.06, 4.25 Hz, 6'-H), 7.58 (1H, d, J = 10.69 Hz, 4-H), 7.79 (1H, d, J = 8.65 Hz, 4'-H), 8.21 (1H, dd, J = 8.06, 2.05 Hz, 5'-H), 8.28 (1H, d, J = 8.65 Hz, 3'-H), 9.12 (1H, dd, J = 4.25, 2.05 Hz, 7'-H), 9.20 (2H, br, NH_2); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 118.9 (=C<), 120.6 (=CH-), 121.1 (=C<), 122.6 (=CH-), 123.5 (=CH-), 128.3 (=CH-), 137.2 (2 x =CH-), 138.7 (=CH-), 138.8 (=CH-), 153.9 (=CH-), 154.2 (=C<), 155.6 (=C<), 163.4 (=C<), 177.1 (=C<).

Anal. Calcd. for $C_{15}H_{11}N_3O$: C, 72.28; H, 4.45; N, 16.86. Found: C, 72.28; H, 4.47; N, 16.75.

2-Amino-7-(1,8-naphthyridin-2-yl)tropone (**23**).

A solution of 7-acetyl-2-aminotropone (**15**) (163 mg, 1.0 mmole) and **2** (134 mg, 1.1 mmoles) in absolute ethanol (4 ml) was stirred for 8 hours at room temperature in the presence of a sodium ethoxide solution, prepared from sodium (46 mg, 2.0 mmoles) and absolute ethanol (2 ml) and worked up as described above to give 2-amino-7-(1,8-naphthyridin-2-yl)tropone (**23**) in a yield of 174 mg (70%) as greenish yellow crystals (from methanol), mp 273-275°; ir (potassium bromide): ν max 3408 (NH), 3264 (NH), 1606 cm^{-1} (C=O); uv (methanol): λ max 215 (log ε 4.41), 243 (4.38), 263 (4.22), 302 (3.99), 319 (3.94), 360 (3.87), 415 nm (4.20); ^1H nmr (deuteriodimethyl sulfoxide): δ 6.76-7.30 (2H, m), 7.57 (1H, dd, J = 8.06, 4.25 Hz, 6'-H), 7.92 (1H, d, J = 8.64 Hz, 4'-H), 7.80-7.96 (2H, m), 8.32 (1H, d, J = 8.64 Hz, 3'-H), 8.40 (1H, dd, J = 8.06, 1.90 Hz, 5'-H), 9.02 (1H, dd, J = 4.25, 1.90 Hz, 7'-H); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 112.1 (=CH-), 120.9 (=CH-), 121.4 (=C<), 122.0 (=CH-), 124.8 (=CH-), 135.5 (=CH-), 136.6 (=C<), 137.1 (=CH-), 137.9 (=CH-), 138.9 (=CH-), 153.0 (=CH-), 155.6 (=C<), 161.1 (=C<), 163.7 (=C<), 172.9 (=C<); ms: m/z (%) 249 (M^+, 100), 221 (58).

Anal. Calcd. for $C_{15}H_{11}N_3O$: C, 72.28; H, 4.47; N, 16.86; M_r^+, 249.0903. Found: C, 72.00; H, 4.46; N, 16.57; M_r^+, 249.0903.

2-Methylamino-7-(1,8-naphthyridin-2-yl)tropone (**24a**).

A solution of 7-acetyl-2-methylaminotropone (**16**) (177 mg, 1.0 mmole) and **2** (134 mg, 1.1 mmoles) in absolute ethanol (4 ml) was stirred for 2 hours at room temperature in the presence of a sodium ethoxide solution, prepared from sodium (46 mg, 2.0 mmoles) and absolute ethanol (2 ml) and worked up as described above to give 2-methylamino-7-(1,8-naphthyridin-2-yl)tropone (**24a**) in a yield of 174 mg (66%) as orange crystals (from methanol), mp 235-236°; ir (potassium bromide): ν max 3250 (NH), 1603 cm^{-1} (C=O); uv (methanol): λ max 216 (log ε 4.35), 247 (4.34), 304 (3.94), 321 (3.88), 362 (3.84), 423 nm (4.22); ^1H nmr (deuteriochloroform): δ 3.12 (3H, d, J = 5.40 Hz, CH_3), 6.55-7.06 (2H, m), 7.25-7.62 (2H, m), 7.82 (1H, br, NH), 8.20-8.50 (4H, m), 9.17 (1H, dd, J = 4.10, 2.00 Hz, 7'-H); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 29.6 (CH_3), 108.5 (=CH-), 120.0 (=CH-), 121.4 (=C<), 121.9 (=CH-), 124.8 (=CH-), 135.4 (=CH-), 135.5 (=C<), 136.9 (=CH-), 137.7 (=CH-), 139.5 (=CH-), 152.9 (=CH-), 155.6 (=C<), 158.6 (=C<), 163.6 (=C<), 173.5 (=C<).

Anal. Calcd. for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 72.78; H, 4.91; N, 15.92.

2-(1,8-Naphthyridin-2-yl)phenol (**25**).

A solution of 2-hydroxyacetophenone (**18**) (136 mg, 1.0 mmole) and **2** (134 mg, 1.1 mmoles) in 50% aqueous methanol (6 ml) was stirred for 7 hours at 65° in the presence of potassium hydroxide (112 mg, 2.0 mmoles). The mixture was quenched with water, acidified with 2*M* hydrochloric acid, and extracted with chloroform. The extract was dried over sodium sulfate and concentrated. The residue was chromatographed on a Wakogel B-10 plate (30 x 30 cm) with chloroform-methanol (50:1) to give 2-(1,8-naphthyridin-2-yl)phenol (**25**) in a yield of 218 mg (98%) as orange crystals (from methanol), mp 195-196° (lit [11], mp 185-187°); ir (potassium bromide): ν max 3510 cm^{-1} (OH); uv (methanol): λ max 220 (log ε 4.37), 255 (4.30), 275 (4.07), 327 (3.98), 356 nm (4.03); ^1H nmr (deuteriochloroform): δ 6.84-7.41 (3H, m, 4-,5-,6-H), 7.47 (1H, dd, J = 8.06, 4.25 Hz, 6'-H), 7.92 (1H, dd, J = 8.03, 1.67 Hz, 3-H), 8.07 (1H, d, J = 8.94 Hz, 4'-H), 8.16 (1H, dd, J = 8.06, 2.05 Hz, 5'-H), 8.27 (1H, d, J = 8.94 Hz, 3'-H), 9.08 (1H, dd, J = 4.25, 2.05 Hz, 7'-H); ^{13}C nmr (deuteriochloroform): δ 118.4 (=CH-), 118.5 (=C<), 118.7 (=CH-), 119.1 (=CH-), 121.1 (=C<), 122.1 (=CH-), 127.2 (=CH-), 132.8 (=CH-), 136.6 (=CH-), 138.3 (=CH-), 153.3 (=C<), 154.1 (=CH-), 161.1 (=C<), 161.5 (=C<); ms: m/z (%) 222 (M^+, 83), 221 (100), 194 (11), 168 (23).

Anal. Calcd for $C_{14}H_{10}N_2O$: M_r^+, 222.0794. Found: M_r^+, 222.0776.

2-(1,8-Naphthyridin-2-yl)aniline (**26**).

A solution of 2-aminoacetophenone (**19**) (135 mg, 1.0 mmole) and **2** (134 mg, 1.1 mmoles) in 50% aqueous methanol (6 ml) was stirred for 7 hours at 65° in the presence of potassium hydroxide (112 mg, 2.0 mmoles) to precipitate a small amount of 2-(1,8-naphthyridin-2-yl)aniline (**26**). The filtrate was extracted with chloroform. The extract was dried over sodium sulfate and concentrated. The residue was chromatographed on a Wakogel B-10 plate (30 x 30 cm) with chloroform-methanol (10:1) to give a major part of the product **26** in a combined yield of 195 mg (88%) as yellow prisms (from methanol), mp 221-222°; ir (potassium bromide): ν max 3421 (NH), 3301 cm^{-1} (NH); uv (methanol): λ max 221 (log ε 4.37), 234 (4.39), 252 (4.26), 303 (3.96), 395 nm (3.86); ^1H nmr (deuteriochlorofom): δ 6.60 (2H, br, NH_2), 6.69-6.87 (2H, m), 7.14-7.33 (1H, m), 7.44 (1H, dd, J = 8.06, 4.25 Hz, 6'-H), 7.76 (1H, dd, J = 8.50, 1.61 Hz, 3-H), 7.95 (1H, d, J = 8.64 Hz, 4'-H), 8.15 (1H, dd, J = 8.06, 2.05 Hz, 5'-H), 8.20 (1H, d, J = 8.64 Hz, 3'-H), 9.08 (1H, dd, J = 4.25, 2.05 Hz, 7'-H); ^{13}C nmr (deuteriochloroform): δ 117.0 (=CH-), 117.5 (=CH-), 119.9 (=C<), 120.7 (=C<), 121.1 (=CH-), 121.5 (=CH-), 129.8 (=CH-), 131.1 (=CH-), 136.6 (=CH-), 137.2 (=CH-), 148.6 (=C<), 153.5 (=CH-), 155.0 (=C<), 162.5 (=C<); ms: m/z (%) 221 (M^+, 42), 220 (100).

Anal. Calcd. for $C_{14}H_{11}N_3$: M_r^+, 221.0954. Found: M_r^+, 221.0934.

2-Methoxy-3-(1,8-naphthyridin-2-yl)tropone (**27**) and 2-Methoxy-7-(1,8-naphthyridin-2-yl)tropone (**28**).

An ethereal solution of diazomethane was added to an ice-cooled solution of 3-(1,8-naphthyridin-2-yl)tropolone (**3a**) (176 mg, 0.7 mmole) in chloroform (20 ml). The mixed solution was allowed to stand for 2 hours in an ice-bath until the resulting solution gave no coloration with iron(III) chloride solution. After removal of the excess of diazomethane and the solvents, the residue was chromatographed on a Wakogel B-10 plate (30 x 30 cm) with ethyl acetate-methanol (10:1).

2-Methoxy-3-(1,8-naphthyridin-2-yl)tropone (**27**) was obtained from the upper fraction in a yield of 100 mg (38%) as pale yellow crystals (from benzene), mp 163-164°; ir (chloroform): ν max 1627 cm^{-1} (C=O); uv (methanol): λ max 224 (log ε 4.39), 249 (4.31), 315 nm (4.19); ^1H nmr (deuteriochloroform): δ 3.81 (3H, s, OCH_3), 7.01-7.59 (4H, m), 7.77 (2H, m), 8.26 (2H m), 9.13 (1H, dd, J = 4.25, 1.90 Hz, 7'-H); ^{13}C nmr (deuteriochloroform): δ 59.5 (OCH_3), 121.7 (=C<), 122.6 (=CH-), 124.4 (=CH-), 129.8 (=CH-), 136.4 (=CH-), 136.5 (=CH-), 136.6 (=CH-), 136.9 (=CH-), 137.2 (=C<), 138.6 (=CH-), 153.7 (=CH-), 155.9 (=C<), 161.8 (=C<), 163.6 (=C<), 182.7 (=C<).

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.45; H, 4.48; N, 10.36.

2-Methoxy-7-(1,8-naphthyridin-2-yl)tropone (**28**) was obtained from the lower fraction in a yield of 132 mg (50%) as yellow crystals (from benzene), mp 183-184°; ir (chloroform): ν max 1607 cm^{-1} (C=O); uv (methanol): λ max 212 (log ε 4.44), 246 (4.36), 309 (3.90), 372 (4.00), 429 (3.49), 456 nm (3.34); ^1H nmr (deuteriochloroform): δ 3.98 (3H, s, OCH_3), 6.73-7.34 (3H, m, 3-,4-,5-H), 7.45 (1H, dd, J = 8.06, 4.25 Hz, 6'-H), 8.01 (1H, d, J = 8.50 Hz, 4'-H), 8.15 (1H, d, J = 8.50 Hz, 3'-H), 8.16 (1H, dd, J = 8.06, 1.90 Hz, 5'-H), 8.37 (1H, dd, J = 10.26, 1.02 Hz, 6-H), 9.07 (1H, dd, J = 4.25, 1.90 Hz, 7'-H); ^{13}C nmr (deuteriochloroform): δ 56.6 (OCH_3), 112.1 (=CH-), 122.1 (=CH-), 122.2 (=C<), 124.2 (=CH-), 127.3 (=CH-), 133.9 (=CH-), 135.8 (=CH-), 136.6 (=CH-), 140.4 (=CH-), 144.0 (=C<), 153.2 (=CH-), 156.1 (=C<), 161.8 (=C<), 166.9 (=C<), 179.2 (=C<).

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.90; H, 4.60; N, 10.48.

Reaction of **3a,b** with Methylamine.

a) A suspended solution of **3a** (125 mg, 0.5 mmole) in 40% aqueous methylamine solution (4 ml) was stirred for 6 days at room temperaturte. Precipitates were collected and washed with methanol to give 2-methylamino-7-(1,8-naphthyridin-2-yl)tropone (**24a**). The filtrate was quenched with water and extracted with chloroform (3 x 30 ml). After the extract was dried over sodium sulfate and concentrated, the residue was chromatographed on a Wakogel B-10 plate (30 x 30 cm) with ethyl acetate-methanol (10:1) to give a major part of **24a** in a combined yield of 109 mg (83%).

b) The reaction of **3b** (264 mg, 1.0 mmole) with 40% aqueous methylamine was carried out and worked up as described above to give 5-methyl-2-methylamino-7-(1,8-naphthyridin-2-yl)tropone (**24b**) in a yield of 250 mg (90%) as red crystals (from methanol), mp 250.5-251.5° ir (potassium bromide): ν max 3275 (NH), 1604 cm^{-1} (C=O); uv (methanol): λ max 215 (log ε 4.43), 250 (4.38), 309 (4.01), 366 (3.89), 438 nm (4.22); ^1H nmr (deuteriochloroform): δ 2.43 (3H, s, 5-CH_3), 3.03 (3H, d, J = 5.42 Hz, N-CH_3), 6.49 (1H, d, J = 10.70 Hz, 3-H), 7.25 (1H, dd, J = 10.70, 0.88 Hz, 4-H), 7.56 (1H, br, NH), 8.08 (1H, d, J = 0.88 Hz, 6-H), 8.13 (1H, d, J = 8.49 Hz, 4'-H), 8.15 (1H, d, J = 8.49 Hz, 3'-H), 8.17 (1H, dd, J = 8.06, 2.05 Hz, 5'-H), 9.08 (1H, dd, J = 4.25, 2.05 Hz, 7'-H); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 24.9 (5-CH_3), 29.5 (N-CH_3), 108.7 (=CH-), 121.4 (=C<), 122.0 (=CH-), 124.9 (=CH-), 129.2 (=CH-), 135.4 (=CH-), 135.6 (=C<), 137.0 (=CH-), 137.6 (=CH-), 141.1 (=CH-), 152.9 (=C<), 155.6 (=C<), 157.3 (=C<), 163.9 (=C<), 172.9 (=C<).

Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.62; H, 5.45; N, 15.15. Found: C, 73.64; H, 5.49; N, 15.13.

Hydrolysis of **24a**.

A solution of **24a** (52 mg, 0.2 mmole) in 50% aqueous methanol (10 ml) was refluxed for 12 hours in the presence of potassium hydroxide (28 mg, 0.5 mmole). The mixture was quenched with water, acidfied with 2*M* hydrochloric acid, and extracted with chloroform. The extract was dried over sodium sulfate and concentrated. The residue was chromatographed on a column containing Wakogel C-200 (10 g) with chloroform-methanol (50:1) to give **3a** in a yield of 43 mg (86%).

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