5-Oxo-1,4-dihydroindenopyridines: Calcium Modulators with Partial Calcium Agonistic Activity

Ulrich Rose*

Institute for Pharmacy, Johannes Gutenberg University of Mainz, Saarstr. 21, D-6500 Mainz, FRG

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The title compounds **4a-g** were prepared by Knoevenagel reactions of 1,3-indandione (**1**) with the aromatic aldehydes **2a-g** followed by cyclizing Michael addition of the products thus obtained with methyl β-aminocrotonate (**3**). The structures of products **4** were characterized by spectal data. Positive inotropic activities were observed on electrically stimulated, left atria of giunea pigs and these effects could be attributed to calcium agonism. On the other hand, barium chloride-induced contractions of guinea pig ileum were inhibited in a dose-dependent manner.

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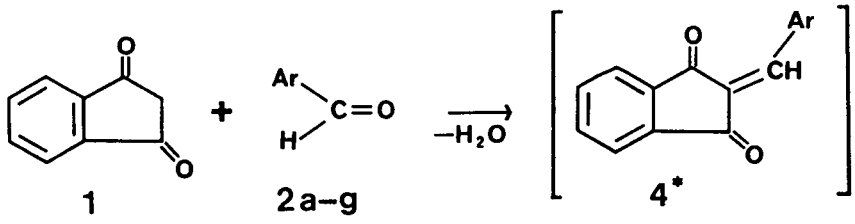
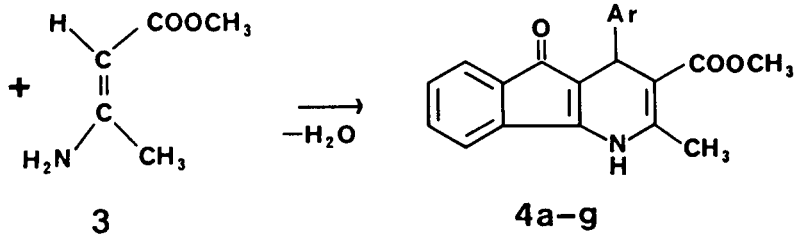
Introduction.

Various different activities on potential-dependent calcium canals can be triggered by attack at dihydropyridine receptors [1]. "Calcium antagonists" of the Nifedipine-type [2,3] cause vascular relaxation as well as reductions of the force of myocardial contraction and frequency by inhibition of calcium influx [4]. At the same time, agonists such as Bay K 8644 and CGP 28392 cause positive inotropic effects and contractions of smooth musculature [5,6]. Recently, anellated dihydropyridines were developed that exhibited selective cardial agonistic activity *in vitro* for the first time while calcium antagonistic effects were observed on smooth musculature [7,8]. In continuation of these investigations, further possibilities for the ring anellation have now been investigated and particular attention was paid to the effects of spatially demanding anellands on receptor binding and intrinsic activity.

Chemical Section.

The target anellated system should possess, in addition to the freely rotatable ester group [9] which is presumed to be essential for receptor binding, a further carbonyl group





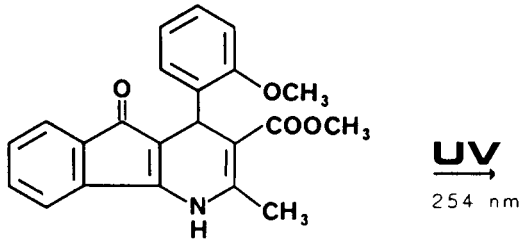
2,4	a	b	c	d	e	f	g
Ar	NO_2	Cl	OCH_3	OCH_3	$O-CH_2$ O	CF_3	$O-CH_2$

Figure 1

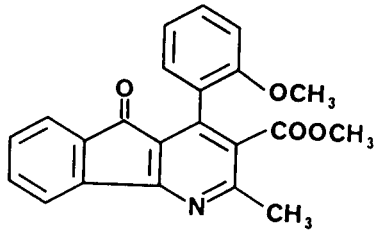
in a rigidly fixed, antiperiplanar orientation to the C=C double bond of the heterocyclic system [10]. The 5-oxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyridine ring system has now been synthesized by means of a three component reaction in analogy to the Hantzsch synthesis [11] (Figure 1).

In this process, methyl β-aminocrotonate (**3**) dissolved in toluene functions as an ambident nucleophile in the cyclizing Michael addition with the condensed Knoevenagel adducts **4**[x] which are prepared in situ from 1,3-indandione (**1**) and the aromatic aldehydes **2a-g**. When the reactions are performed in ethanol solution they come to a standstill at the stage of the benzylidene-1,3-indandiones (**4**[x]) which also remain insoluble on heating.

Under the action of light, decomposition processes are observed in the cases of **4a-g** (dissolved in dichloromethane) and tlc monitoring indicates that a new predominant product is formed in each case. The rates of these photoreactions can be increased considerably by exposure to uv irradiation. Thus, for example, after 4 days exposure to uv light (λ = 254 nm) **4c** was converted almost quantitatively into the new product **4h** in which the dihydropyridine (DHP) ring of **4c** has been oxidized to a pyridine ring (Figure 2).



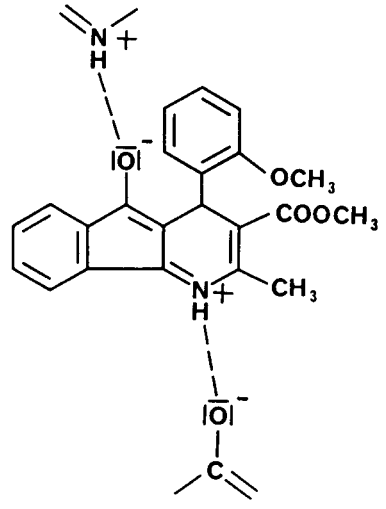
4c



4h

Figure 2

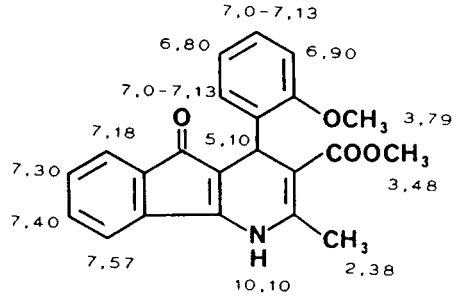
The structures postulated for **4a-g** have been confirmed by spectroscopic data. The ir spectra exhibit absorption bands for the secondary amino group between 3200 and 3300 cm^{-1}, in addition, aromatic and aliphatic CH stretching absorptions as well as C=C stretching absorptions are observed in the expected wave number regions. In the solid state (product **4c**), the ester carbonyl function absorbs at 1700 cm^{-1} and the ketone carbonyl group (absorption II) at 1630 cm^{-1}. This shift to the lower wave number region is indicative of the existence of a resonance structure stabilized by intermolecular hydrogen bonds (Figure 3).



4c

Figure 3

Such valency isomerizations accompanied by shifts of the absorption bands to lower wave numbers are also known for other β-diketones and β-aminoketones [12-14]. Intermolecular hydrophilic interactions can be suppressed by transferring the substance into a lipophilic solvent. Accordingly, in chloroform solution, the ketone band of **4c** is shifted to 1660 cm^{-1} and the NH absorption to 3420 cm^{-1}. The ^{1}H-nmr spectrum of **4c** exhibits the resonances illustrated in Figure 4.



4c

Figure 4

The resonances of the aromatic protons were unequivocally assigned with the help of increment calculations, analyses of spin-spin couplings, homonuclear ^{1}H{^{1}H}-NOE measurements, and spin decoupling experiments. Cleavage of the $C_6H_4R^{\cdot}$ radical from the molecular ion was the predominant fragmentation process observed in the EI

mass spectra.

Pharmacological Section.

1. Materials and Methods.

a) Investigations on Isolated, Electrically Stimulated, Left Atria of Guinea Pigs.

Healthy guinea pigs of either sex with body weights of 250-450 g were killed by a blow to the neck and exsanguinated. After opening of the thorax, the hearts were removed and immediately transferred to the Tyrode solution at 37° under perfusion with oxygen. The left atria were prepared and fixed on a DMS detector type TF 6 V5 (Fleck, Mainz/FRG) in an organ bath of 50 ml capacity between two platinum electrodes (Fleck, Mainz/FRG). The liquid in the bath consisted of an oxygen-perfused Tyrode solution at 37° having the following composition: sodium chloride 10.0, potassium chloride 0.25, calcium chloride dihydrate 0.33, magnesium chloride hexahydrate 0.27, sodium bicarbonate 1.0, sodium dihydrogenphosphate dihydrate 0.65, glucose 1.0 g in 1000 ml of water (*p*H 7.7). The electrical stimulation was performed at a frequency of 1 Hz with square wave impulses of 2 ms and a potential of 30 V. The isometrically measured impulses under a preloading of 0.5 g were recorded on a direct recorder after electrical amplification (Hellige TF 19). After an equilibration period of 30 minutes, the concentration-activity curves of the individual substances to be tested were recorded using the cumulative technique [15] (seven values in the dose range $1 \cdot 10^{-7}$ to $1 \cdot 10^{-4}$ mol/l). In order to investigate the DHP receptor selectivity, concentration-activity curves for Nifedipine in the presence and absence of the agonists under test were also determined. A fresh organ was used for each experiment; for the number of experiments, see Tables 1 and 2.

EC_{50} value; The dose which brings about 50% of the maximum effect.

Intrinsic activity: The ratio of the maximum effect of each substance to the maximum effect of CGP 28392.

b) Investigations on Isolated Ileum of Guinea Pigs.

Healthy guinea pigs of either sex with body weights of 250-450 g (see under 1a above) were killed by a blow to the neck and exsanguinated. After opening of the abdominal cavity, parts of the small intestine were removed, freed from mesenteric tissue, and stored for 3 hours in Tyrode solution (for composition, see above) at 37° under perfusion with oxygen. Subsequently, 3 cm lengths of intenstine were fastened to a DMS detector type TF3 V3 (Fleck, Mainz/FRG) (preloading 0.56 g) in an organ bath of 50 ml capacity. Measurement of the contraction effects was achieved after amplification using a Hellige preamplifier TF 19 with the aid of a Rika-Denki electronic recorder (3-pen recorder). The liquid in the bath again consisted of oxygen-perfused Tyrode solution at 37°. In order to check for antagonistic effects, contractions were induced with barium chloride ($4 \cdot 10^{-3}$ mol/l, bath concentration). After thorough washing out, this process was repeated until the amplitude of the contraction became constant. Investigations of the substances to be tested were performed using the single dose technique in which the barium chloride contractions were induced after addition of the test substance and 5 minutes exposure time. Between administrations of the individual substances, the preparation was washed until the initial situation had been reestablished and the barium chloride contractions were then induced.

EC_{50} value: The dose which brings about 50% of the maximum effect.

Intrinsic activity: The ratio of the maximum effect of each substance to the maximum effect of Nifedipine.

2. Results.

The substances **4a-g** investigated exhibited ambivalent actions on electrically stimulated, left atria and ileum of guinea pigs. Barium chloride-induced contractions of the ileum were dose-dependently inhibited by all compounds **4a-g** (Table 1).

Table 1

EC_{50} Values and Intrinsic Activity on Ileum

Compound	EC_{50} (mol/l)	Maximum Effect [%] [1]	Intrinsic Activity [2]	n [3]
Nifedipine	$2 \cdot 10^{-8}$	95 ± 2.8	1	9
4a	$1.4 \cdot 10^{-5}$	71 ± 8.6	0.75	3
4b	$5 \cdot 10^{-6}$	62 ± 7.8	0.65	3
4c	$7.5 \cdot 10^{-7}$	98 ± 1.4	1.03	3
4d	$3.5 \cdot 10^{-5}$	51 ± 14.0	0.54	2
4e	–	9	0.09	2
4f	$2.4 \cdot 10^{-6}$	84 ± 11.0	0.88	3
4g	$5.3 \cdot 10^{-5}$	28 ± 2.5	0.29	3

[1] Contraction inhibition $\bar{x}$ ± S.E.M.
[2] Nifedipine = 1.
[3] Number of experiments.

Higher activities were observed for those compounds in which rotation of the aromatic group at the 4-position is hindered by the presence of sterically demanding substituents on its *ortho*-positions (**4c, f**); intrinsic activity values comparable to that of Nifedipine were attained, the reduced receptor affinities are apparent from the EC_{50} values.

Compounds **4a-g** exerted positive inotropic effects on electrically stimulated, left atria (Table 2).

Table 2

EC_{50} Values and Intrinsic Activity on Electrically Stimulated, Left Atria

Compound	EC_{50} (mol/l)	Maximum Effect [%] [1]	Intrinsic Activity [2]	n [3]
CGP 28392	$7.9 \cdot 10^{-6}$	452 ± 43.7	1	3
4a	$1.1 \cdot 10^{-5}$	245 ± 65.5	0.54	5
4b	$1 \cdot 10^{-5}$	142 ± 31.9	0.31	4
4c	$3.2 \cdot 10^{-6}$	115 ± 18.9	0.25	3
4d	$8.4 \cdot 10^{-6}$	149 ± 22.2	0.33	5
4e	$1.3 \cdot 10^{-6}$	76 ± 11.6	0.17	3
4f	$6.3 \cdot 10^{-7}$	44 ± 4.7	0.1	2
4g	$1 \cdot 10^{-5}$	102 ± 13.2	0.23	5

[1] Increase in contractility $\bar{x} \pm$ S.E.M.
[2] CGP 28392 = 1.
[3] Number of experiments.

The highest intrinsic activity with a value of 0.54 (referred to CGP 28392) was observed for **4a** while some of the EC_{50} values were in the region of the standard and the others were somewhat higher. Some of the concentration-activity curves show a biphasic course, *i.e.* antagonistic effects were observed at a bath concentration in excess of $1 \cdot 10^{-4}$ mol/l. Preadministration of propranolol ($3 \cdot 10^{-7}$ mol/l) did not give rise to a weakening of the activity of **4a**; hence, stimulation of β-adrenergic receptors can be excluded. After preadministration of **4a**, a left-shift of the subsequently recorded isoprenaline dose-activity curve was not observed and, therefore, a phosphodiesterase inhibition can also be ruled out as a possible cause of the positive inotropic activity [16]. The dose-activity curve of Nifedipine on electrically stimulated, left atria after preadministration of **4a** ($1 \cdot 10^{-4}$ mol/l) was concomitantly shifted to the right and this is indicative of a competitive antagonism at the DHP receptors. In the receptor binding test at EC_{50} values of $> 1 \cdot 10^{-6}$ mol/l (**4f**) and $6 \cdot 10^{-7}$ mol/l (**4a**), a ^{3}H-nitrendipine expulsion was detected, albeit with only a somewhat weaker activity in comparison to that of the standard Nifedipine. On the smooth, potassium chloride (40 mmoles/l bath concentration) stimulated, aorta musculatore (rabbit), **4a** at a dosage of $1 \cdot 10^{-6}$ mol/l bath concentration showed a 60% inhibition of contraction and **4f** in the same experiment a 71% inhibition of contraction. Thirty minutes after intraduodenal administration of **4f** (25 mg/kg in rat), 9% decreases of the systolic and diastolic pressures were determined. In a screening test, compound **4b** was proven to be an antagonist of substance P (2 μg/ml).

Discussion.

The oxoindenodihydropyridines prepared by a variation of the Hantzsch synthesis exhibited differing, organ-specific activities at DHP receptors. By means of modulation of the Ca^{2+} influx they developed calcium antagonistic activities of smooth musculature (ileum, aorta) whereas, in contrast, they developed positive inotropic activities on the left atria as a result of calcium agonism. Qualitatively, these activities correspond to those of the more thoroughly investigated hexahydroquinolinones [7,8]; however, the intrinsic activities at all organs are reduced in comparison to those of the hexahydroquinolinones. The anellation by spatial demanding anellands such as 1,3-indandione, therefore, rather has disadvantageous effects on the quality of the activity in comparison to those achieved using alicyclic 1,3-diketones.

The relatively low stabilities of the tested compounds in solution towards the action of light is worthy of note.

EXPERIMENTAL

Melting points were taken with a Büchi SMP 20 melting point apparatus according to Dr. Tottoli and are not corrected. The ir spectra were taken on Beckmann spectrophotometers IR-33 and IR-4220. The ^{1}H-nmr spectra were taken on Varian EM 360 and Bruker AM 400 spectrometers, TMS as internal standard. The mass spectra were observed on a Varian MAT CH 7A (Bremen/FRG). The tlc, cc, and pcc were taken on silica gel (Merck) of various activity grades.

Methyl 2-Methyl-4-(3-nitrophenyl)-5-oxo-1,4-dihydro-5*H*-indeno-[1,2-*b*]pyridine-3-carboxylate (**4a**).

A mixture of 4.38 g (30 mmoles) of 1,3-indandione (**1**), 4.5 g (30 mmoles) of 3-nitrobenzaldehyde (**2a**), and 3.45 g (30 mmoles) of methyl 3-aminocrotonate (**3**) dissolved in 120 ml of toluene was heated under reflux for 4 hours. The crude product, which precipitated on cooling, was dissolved in 100 ml of hot methanol, active charcoal was added, and the mixture was boiled for a short time. The active charcoal was filtered from the hot mixture, the product was precipitated by cooling and addition of water, and recrystallized several times from ethanol/water. Red platelets with mp 248° were obtained in a yield of 2.25 g (20%); ir (potassium bromide): 3210, 3200 (NH stretch), 3080, 3010 (aromatic CH stretch), 2950, 2920 (aliphatic CH stretch), 1700 (C=O stretch), 1630 (C=O stretch II), 1580, 1530, 1500 cm^{-1} (phenyl C=C stretch); ^{1}H nmr (deuteriochloroform): δ (ppm) = 2.55 (s, 3H, C*H*$_3$ in 2-position), 3.6 (s, 3H, COOC*H*$_3$), 5.1 (s, 1H, *H* at C-4), 6.75 (s, 1H, N*H*, exchangeable with deuterium oxide), 7.25-7.5 (m, 4 H, *H* of anellated phenyl ring), 7.6-8.4 (m, 4H, *H* of substituted phenyl ring); ms: (100 eV) m/z = 376 (19%, $M^{+\cdot}$), 374 (92%, $M^{+\cdot} - H_2$), 357 (100%, 374 - OH·), 343 (31%, 374 - OCH_3·), 327 (62%, 374 - HNO_2), 254 (62%, 376 - $C_6H_4NO_2$·), 222 (23%, 254 - CH_3OH).

Anal. Calcd. for $C_{21}H_{16}N_2O_5$ (376.2): C, 67.0; H, 4.3; N, 7.4. Found: C, 66.9; H, 4.3; N, 7.7.

Methyl 4-(2-Chlorophenyl)-2-methyl-5-oxo-1,4-dihydro-5*H*-indeno-[1,2-*b*]pyridine-3-carboxylate (**4b**).

Product **4b** was obtained by heating a solution of 3.65 g (25 mmoles) of **1**, 3.51 g (25 mmoles) of 2-chlorobenzaldehyde (**2b**),

and 2.88 g (25 mmoles) of **3** in toluene for 12 hours at 80°. After repeated recrystallizations from ethanol/water, red platelets with mp 280° were obtained in a yield of 1.38 g (15%); ir (potassium bromide): 3280 (NH stretch), 1700 (C=O stretch), 1645 (C=O stretch II), 1590, 1510 cm^{-1} (phenyl C=C stretch); ^{1}H-nmr (deuteriochloroform): δ (ppm) = 2.73 (s, 3H, C*H*$_3$ at 2-position), 3.54 (s, 3H, COOC*H*$_3$), 5.1 (s, 1H, *H* at C-4), 7.15-7.9 (m, 9H, *H* of aromatic rings and N*H*, exchangeable with deuterium oxide); ms: (100 eV) m/z = 365 (11%, M^+), 350 (6%, M^+ - CH_3·), 254 (100%, M^+ - C_6H_4Cl·), 222 (16%, 254 - CH_3OH), 194 (14%, 254 - $HCOOCH_3$).

Anal. Calcd. for $C_{21}H_{16}ClNO_3$ (365.2): C, 69.1; H, 4.4; N, 3.8. Found: C, 69.1; H, 4.4; N, 3.6.

Methyl 4-(2-Methoxyphenyl)-2-methyl-5-oxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyridine-3-carboxylate (**4c**).

A solution of 3.65 g (25 mmoles) of **1**, 3.4 g (25 mmoles) of 2-methoxybenzaldehyde (**2c**), and 2.88 g (25 mmoles) of **3** in 150 ml of toluene was heated for 12 hours under reflux at 80°. The mixture was allowed to cool, the crude product was filtered off, and worked up as described above for **4b**. Red needles with 259° were obtained in a yield of 1.65 g (18%); ir (potassium bromide): 3250, 3220, 3180 (NH stretch), 3070 (aromatic CH stretch), 2940 (aliphatic CH stretch), 1700 (C=O stretch), 1630 (C=O stretch II), 1580, 1510 cm^{-1} (phenyl C=C stretch); ^{1}H-nmr (DMSO-d_6): δ (ppm) = 2.38 (s, 3H, C*H*$_3$ at 2-position), 3.48 (s, 3H, COOC*H*$_3$), 3.79 (s, 3H, OC*H*$_3$ at 2-position of phenyl ring), 5.1 (s, 1H, *H* at C-4), 6.8 (t, 1H, *H*-5 of substituted phenyl ring, ^3J = 8 Hz), 6.9 (d, 1H, *H*-3 of substituted phenyl ring, ^3J = 8 Hz), 7.0-7.12 (m, 2H, *H*-4 and *H*-6 of substituted phenyl ring), 7.18 (d, 1H, *H*-6 of anellated phenyl ring, ^3J = 8 Hz), 7.3 (t, 1H, *H*-7 of anellated phenyl ring, ^3J = 8 Hz), 7.4 (t, 1H, *H*-8 of anellated phenyl ring, ^3J = 8 Hz)*, [*7.57 (d, 1H, *H*-9 of anellated phenyl ring, ^3J = 8 Hz)], 10.1 (s, 1H, N*H*, exchangeable with deuterium oxide); ms: (100 eV) m/z = 361 (19%, M^+), 359 (90%, M^+ - H_2), 344 (15%, 359 - CH_3·), 328 (55%, 359 - OCH_3·), 327 (30%, 359 - CH_3OH), 300 (100%, 359 - $COOCH_3$·), 254 (15%, M^+ - C_7H_7O·).

Anal. Calcd. for $C_{22}H_{19}NO_4$ (361.2): C, 73.2; H, 5.3; N, 3.9. Found: C, 73.3; H, 5.3; N, 3.6.

Methyl 4-(3-Methoxyphenyl)-2-methyl-5-oxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyridine-3-carboxylate (**4d**).

Product **4d** was obtained by heating a mixture of 4.38 g (30 mmoles) of **1**, 4.08 g (30 mmoles) of 3-methoxybenzaldehyde (**2d**), and 3.45 g (30 mmoles) of **3** in 150 ml of toluene for 14 hours under reflux and then working-up the reaction mixture as described for **4b**. Red needles with mp 210° were obtained in a yield of 1.82 g (17%); ir (potassium bromide): 3280, 3240 (NH stretch), 3020 (aromatic CH stretch), 2960, 2840 (aliphatic CH stretch), 1705 (C=O stretch), 1640 (C=O stretch II), 1590, 1510 cm^{-1} (phenyl C=C stretch); ^{1}H-nmr (deuteriochloroform): δ (ppm) = 2.5 (s, 3H, C*H*$_3$ in 2-position), 3.6 (s, 3H, COOC*H*$_3$), 3.8 (s, 3H, OC*H*$_3$ at C-2 of phenyl ring), 5.0 (s, 1H, *H* at C-4), 6.5-7.6 (9H, *H* aromatic and N*H*, exchangeable with deuterium oxide); ms: (100 eV) m/z = 361 (16%, M^+), 359 (4%, M^+ - H_2), 346 (4%, M^+ - CH_3·), 330 (4%, M^+ - OCH_3·), 302 (7%, 361 - $COOCH_3$·), 254 (100%, M^+ - C_7H_7O·), 222 (8%, 254 - CH_3OH), 194 (14%, 254 - $HCOOCH_3$).

Anal. Calcd. for $C_{22}H_{19}NO_4$ (361.2): C, 73.2; H, 5.3; N, 3.9. Found: C, 72.9; H, 5.4; N, 3.6.

Methyl 2-Methyl-4-[(3,4-methylenedioxy)phenyl]-5-oxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyridine-3-carboxylate (**4e**).

Compound **4e** was prepared analogously to **4a** by heating 4.38 g (30 mmoles) of **1**, 4.5 g (30 mmoles) of 3,4-methylenedioxybenzaldehyde (**2e**), and 3.45 g (30 mmoles) of **3** in 150 ml of toluene for 11 hours at 80°. Isolation and purification were carried out as described for **4b**. Red platelets with mp 282° dec, were obtained in a yield of 2.11 g (19%); ir (potassium bromide): 3270, 3220 (NH stretch), 2940, 2890 (aliphatic CH stretch), 1705 (C=O stretch), 1635 (C=O stretch II), 1580, 1505 cm^{-1} (phenyl C=C stretch); ^{1}H-nmr (deuteriochloroform): δ (ppm) = 2.5 (s, 3H, C*H*$_3$ at 2-position), 3.6 (s, 3H, COOC*H*$_3$), 4.9 (s, 1H, *H* at C-4), 5.85 (s, 2H, *H* of methylenedioxy group), 6.5 (s, 1H, N*H*, exchangeable with deuterium oxide), 6.7-7.7 (m, 7H, *H* aromatic); ms: (100 eV) m/z = 375 (17%, M^+), 360 (3%, M^+ - CH_3·), 316 (4%, M^+ - $COOCH_3$·), 254 (100%, M^+ - $C_7H_5O_2$·), 222 (9%, 254 - CH_3OH), 194 (13%, 254 - $HCOOCH_3$).

Anal. Calcd. for $C_{22}H_{17}NO_5$ (375.2): C, 67.2; H, 4.8; N, 3.6. Found: C, 67.2; H, 5.0; N, 3.6.

Methyl 4-[(2-Trifluoromethyl)phenyl]-2-methyl-5-oxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyridine-3-carboxylate (**4f**).

A solution of 4.38 g (30 mmoles) of **1**, 5.22 g (30 mmoles) of 2-trifluoromethylbenzaldehyde (**2f**), and 3.45 g (30 mmoles) of **3** in 150 ml of toluene was treated with a few drops of pyridine and then heated for 9 hours under reflux. Work-up as described above for **4b** gave red platelets with mp 283° in a yield of 3.05 g (25%); ir (potassium bromide): 3320 (NH stretch), 3070 (aromatic CH stretch), 2950 (aliphatic CH stretch), 1700 (C=O stretch), 1635 (C=O stretch II), 1580, 1500 cm^{-1} (phenyl C=C stretch); ^{1}H-nmr (deuteriochloroform): δ (ppm) = 2.5 (s, 3H, C*H*$_3$ at 2-position), 3.5 (s, 3H, COOC*H*$_3$), 5.4 (s, 1H, *H* at C-4), 6.5 (s, 1H, N*H*, exchangeable with deuterium oxide), 7.05-7.9 (m, 8H, *H* aromatic); ms: (100 eV) m/z = 399 (2%, M^+), 384 (2%, M^+ - CH_3·), 340 (2%, 399 - $COOCH_3$·), 254 (100%, M^+ - $C_7H_4F_3$·), 222 (4%, M^+ - CH_3OH), 194 (5%, 254 - $HCOOCH_3$).

Anal. Calcd. for $C_{22}H_{16}F_3NO_3$ (399.2): C, 66.2; H, 4.0; N, 3.5. Found: C, 66.2; H, 4.2; N, 3.6.

Methyl [3-(Benzyloxy)phenyl]-2-methyl-5-oxo-1,4-dihydro-5*H*-indeno[1,2-*b*]pyridine-3-carboxylate (**4g**).

A solution of 4.38 g (30 mmoles) of **1**, 6.36 g (30 mmoles) of 3-benzyloxybenzaldehyde (**2g**), and 3.45 g (30 mmoles) of **3** in 150 ml of toluene was boiled for 13 hours and then worked-up as described above for **4b**. Red needles with mp 214° were obtained in a yield of 1.71 g (13%); ir (potassium bromide): 3260, 3220, 3190 (NH stretch), 3070 (aromatic CH stretch), 2950, 2890 (aliphatic CH stretch), 1700 (C=O stretch), 1630 (C=O stretch II), 1580, 1500 (phenyl C=C stretch); ^{1}H-nmr (deuteriochloroform): δ (ppm) = 2.4 (s, 3H, C*H*$_3$ at 2-position), 3.55 (s, 3H, COOC*H*$_3$), 4.9 (s, 2H, C*H*$_2$ of benzyl group), 5.0 (s, 1H, *H* at C-4), 6.8 (s, 1H, N*H*, exchangeable with deuterium oxide), 6.9-7.9 (m, 13 H, *H* aromatic); ms: (100 eV) m/z = 437 (6%, M^+), 346 (2%, M^+ - C_7H_7·), 254 (100%, M^+ - $C_{13}H_{11}O$·), 222 (4%, 254 - CH_3OH), 194 (6%, 254 - $HCOOCH_3$).

Anal. Calcd. for $C_{28}H_{23}NO_4$ (437.3): C, 76.9; H, 5.3; N, 3.2. Found: C, 76.6; H, 5.4; N, 3.1.

Methyl 4-(2-Methoxyphenyl)-2-methyl-5-oxo-5*H*-indeno[1,2-*b*]pyridine-3-carboxylate (**4h**).

A solution of **4c** in dichloromethane was subjected to uv irradiation (λ = 254 nm) for 4 days. The newly formed product was separated and purified by column chromatography using dichloromethane as the mobile phase. A yellow powder with mp 183° was obtained; ^{1}H-nmr (DMSO-d_6): δ (ppm) = 2.59 (s, 3H, CH_3 at 2 position), 3.55 (s, 3H, COOCH_3), 3.64 (s, 3H, OCH_3 at phenyl C-2), 6.95-7.4 (m, 4H, *H* of substituted phenyl ring), 7.55-7.9 (m, 4H, *H* of anellated phenyl ring); ms: (90 eV), m/z = 359 (100%, M^+), 344 (10%, M^+ - CH_3·), 328 (65%, M^+ - OCH_3·), 300 (93%, M^+ - $COOCH_3$·).

2-[(2-Methoxy)benzylidene]-1,3-indandione (**4^x**) [17].

A solution of 1.46 g (10 mmoles) of 1,3-indandione (**1**) and 2-methoxybenzaldehyde (**2c**) in ethanol was warmed gently for 3 hours and then stirred at room temperature for 10 hours. The product **4^x** with mp >200° dec, was recrystallized from ethanol/-water and obtained in a yield of 1.2 g (45%); ir (potassium bromide): 1720, 1690 (C=O stretch), 1580 cm^{-1} (phenyl C=C stretch); ^{1}H-nmr (DMSO-d_6): δ (ppm) = 3.9 (s, 3H, OCH_3), 7.2-8.1 (m, 8H, *H* aromatic), 8.35 (s, 1H, *H* of vinyl group); ms: (100 eV) m/z = 264 (25%, M^+), 233 (100%, M^+ - OCH_3·).

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