Synthesis and antispasmodic effect of aryl substituted *N*-carbamoyl/thiocarbamoyl isoquinolines

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Dedicated to Prof. T. R. Govindachari on the occasion of his 85th birthday
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Abstract
A reaction of tetrahydropapaverine obtained from homoveratryl amine and homoveratric acid by three step procedure with various aromatic isocyanates or isothiocyanates to give the corresponding aryl substituted N-carbamoyl or N-thiocarbamoyl derivatives of isoquinoline has been achieved. All the compounds have been screened for their antispasmodic activities.

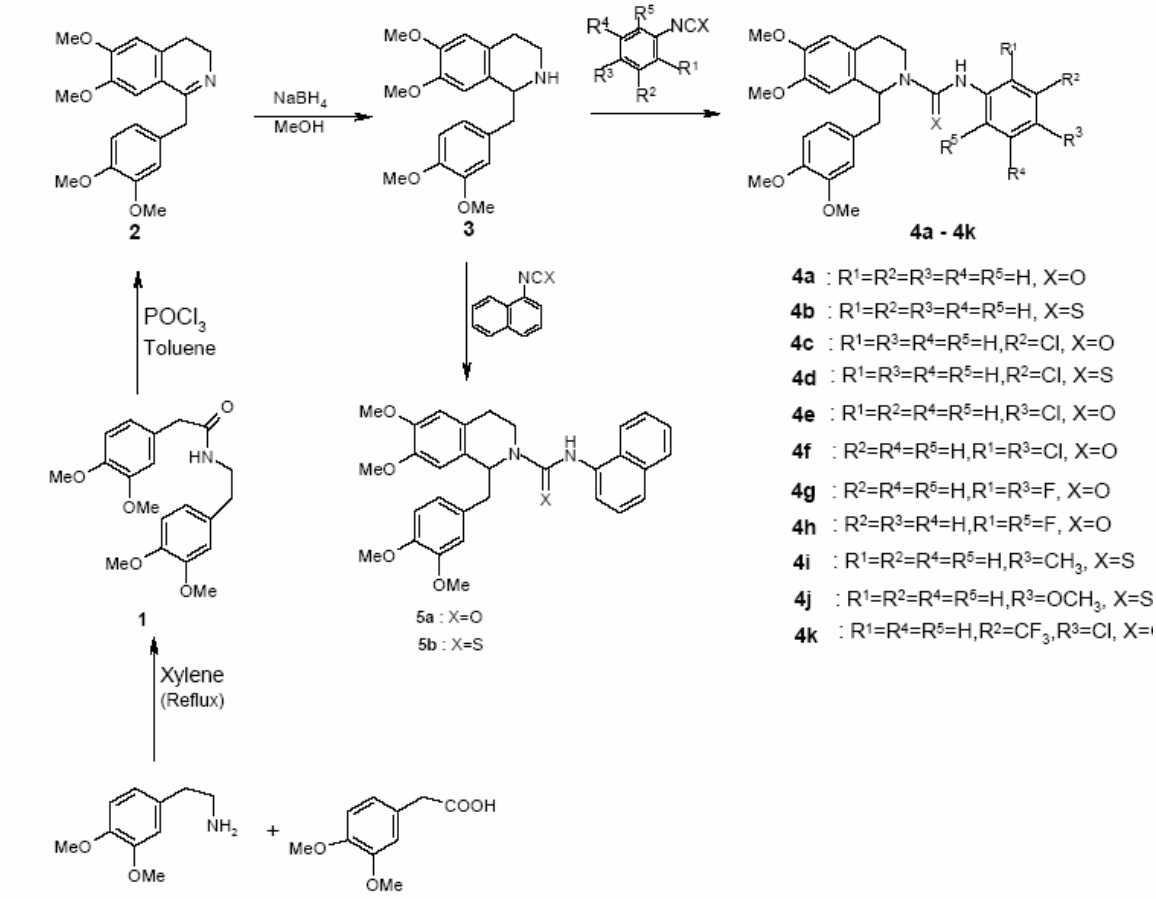
Keywords: Isoquinoline, papaverine, tetrahydropapaverine, antispasmodic activity, isocyanates/isothiocyanates

Introduction

The chemistry of tetrahydroisoquinoline alkaloids has attracted considerable interest over the years due to their potent biological activities. A wide range of N- substituted 1,2,3,4-tetrahydroisoquinolines has been found to be a useful starting materials for the construction of a variety of medically attractive intermediates.[1-4] The natural alkaloids are generally optically active compounds possessing antihypertensive, hemostatic, smooth or skeletal muscle relaxant, antispasmodic, antitussive, antimalarial, narcotic, analgesic or antipyretic activities[5]. The aporphine alkaloids namely (±) thaliporphine, (±) N-methylaurotetanine, (±) isoboldine have been found to be of significant biological and biogenetic interest[6,7]. Papaverine is also a naturally occurring benzylisoquinoline alkaloid isolated from opium. Clinically, papaverine is employed as a vasodilator because of its relaxatory effect on vascular smooth muscle[8,9]. Few N-acyl derivatives of papaverine and related compounds show variety of activities against AIDS, glucoma and fungal infections[10-12]. In quest for biologically more potent compounds we envisioned to synthesize aryl substituted N-carbamoyl as well as N-thiocarbamoyl derivatives of tetrahyropapaverine. In this paper, we report a four step procedure that gives aryl substituted N-carbamoyl or N-thiocarbamoyl derivatives of tetrahydropapaverine and studied their antispasmodic activity.

Results and Discussion

Compounds **4a**–**4k**, **5a** and **5b** were synthesized by the reaction of tetrahydropapaverine **3**, which in turn prepared from **2**, with the corresponding substituted aryl isocyanates and substituted aryl isothiocyanates (Scheme 1). Amide **1** was prepared by the condensation of homoveratryl amine and homoveratric acid in xylene with azeotropic removal of water.



Scheme 1

Cyclization of **1** to 3,4-dihydroisoquinoline **2** was achieved in a Bischler – Napierlski fashion, in refluxing toluene with phosphorous oxychloride. Reduction of 3,4-dihydroisoquinoline with $NaBH_4$ in methanol resulted in the formation of tetrahydropapaverine **3**.[13] ^{1}H NMR and I.R. spectra obtained for these compounds were consistent with those reported earlier. Treatment of tetrahydropapaverine **3** with *p*-chlorophenyl isocyanate in CH_3CN resulted in the formation of 1-(3,4-dimethoxybenzyl)-2-(4-chlorophenylcarbamoyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **4e,** mp 108 ˚C in 87% yield. The proton magnetic resonance spectrum of product **4e** showed aromatic protons as two singlets, one multiplet and two double-doublets at δ6.52(s, 1H), 6.65(s, 1H), 6.74-6.87(m,3H), 6.88,6.91(dd, 2H, *J* = 8.4Hz), 7.13, 7.15(dd, 2H, *J* = 8.4Hz) respectively. A broad singlet is shown by (CONH) proton at δ5.61 (br s, 1H). The ArCHN proton showed a multiplet at δ4.98(m,1H).The four methoxy group protons

showed three singlets at δ3.81(s,3H), 3.85(s,6H) and 3.87(s,3H). The four other saturated cyclic ring protons of isoquinoline ring moiety (NCH_2CH_2) showed as multiplets located around δ2.93-3.39 (m, 4H). The two $ArCH_2$ hydrogens showed a multiplet at δ2.66-2.71 (m, 2H).

Table 1. Physical and spectral data of compounds **4a-4k** and **5a-5b**

Compound	mp (˚C)	Yield (%)	Molecular Formula (M. W.)	MS (m/z)	IR (KBr) $\nu_{max}(cm^{-1})$
4a	105 -106	90	$C_{27}H_{30}N_2O_5$ (462)	463 $(M+H)_+$	3373 (NH), 1654 (CO).
4b	125 -126	89	$C_{27}H_{30}N_2O_4S$ (478)	479 $(M+H)_+$	3335 (NH), 1324 (CS).
4c	96 -97	87	$C_{27}H_{29}ClN_2O_5$ (496)	497 $(M+H)_+$	3351 (NH), 1653 (CO).
4d	75 -76	80	$C_{27}H_{29}ClN_2O_4S$ (512)	513 $(M+H)_+$	3375 (NH), 1290 (CS).
4e	108 -109	87	$C_{27}H_{29}ClN_2O_5$ (496)	497 $(M+H)_+$	3360 (NH), 1655 (CO).
4f	65 -66	82	$C_{27}H_{28}Cl_2N_2O_5$ (530)	531 $(M+H)_+$	3389 (NH), 1669 (CO).
4g	63 -64	83	$C_{27}H_{28}F_2N_2O_5$ (498)	499 $(M+H)_+$	3358 (NH), 1651 (CO).
4h	60 -61	85	$C_{27}H_{28}F_2N_2O_5$ (498)	499 $(M+H)_+$	3385 (NH), 1654 (CO).
4i	135 -136	82	$C_{28}H_{32}N_2O_4S$ (492)	493$(M+H)_+$	3338 (NH), 1258 (CS).
4j	80 -81	79	$C_{28}H_{32}N_2O_5S$ (508)	509 $(M+H)_+$	3398 (NH), 1237 (CS).
4k	182 -183	81	$C_{28}H_{28}ClF_3N_2O_5$ (564)	564 $(M+H)_+$	3340 (NH), 1659 (CO).
5a	158 -159	80	$C_{31}H_{32}N_2O_5$ (512)	513 $(M+H)_+$	3331 (NH), 1595 (CO).
5b	150 -151	78	$C_{31}H_{32}N_2O_4S$ (528)	529 $(M+H)_+$	3331 (NH), 1323 (CS).

The IR absorption bands at 3360(NH), 1655(CO) cm^{-1} supports the presence of NH and CO functionalities within the molecule. This conclusion that the product **4e** was formed by the condensation of **3** with 4-chlorophenyl isocyanate moieties was based on the presence of a pseudo or quasimolecular ion with the mass fragmentation of this compound. The product **4e** showed two prominent $(M+H)^+$ and $(M+Na)^+$ ion peaks in the MALDI-MS fragmentation ions at *m/*z 497 and 519 respectively. Similarly, products **4a-4k** along with **5a-5b** were obtained in 80-90% yield and were purified by column chromatography. These compounds were characterized on the basis of their ^{1}HNMR, mass spectral data and IR absorption bands. The physical and spectral data as obtained for these compounds have been found consistent and is reported in Table 1 and Table 2 respectively.

Antispasmodic activity

The work includes muscle relaxation studies on isolated guinea pig ileum, contracted with acetylcholine[14-15]. Guinea pigs (n = 6) of both sexes (300 – 500 g) were used for this study. The animals were killed by a blow to the head, the ileum was removed immediately and placed in aerated Krebs saline at 37 ^{o}C. This saline contained (in mM): NaCl, 120.7; KCl, 5.9; $CaCl_2$, 2.5; $MgCl_2$, 1.2; $NaHCO_3$, 15.5; and glucose, 11.5 at pH 7.3. For tension recording 2 cm ileal strips were mounted in a 10 mL organ bath and were connected to physiograph (Polyrite, Recorders

and Medicare systems) through force tension transducer. In the concentration range 10μM - 150μM papaverine and all its derivatives caused relaxation of spontaneous rhythmic contractions of both guinea pig ileum accompanied by a fall in resting tension.

Table 2. ^{1}H NMR spectral data of compounds **4a-4k** and **5a-5b**

Compound	$_{1}$H NMR $CDCl_3$(δ ppm)
4a	2.93-2.96(m, 2H, $ArCH_2$), 3.02-3.40(m, 4H, NCH_2CH_2), 3.80(s, 3H, OCH_3), 3.85(s, 6H, 2 x OCH_3), 3.87(s, 3H, OCH_3), 5.03(m, 1H, ArCHN), 5.68 (br s, 1H, NH), 6.50(s, 1H, ArH), 6.65(s, 1H, ArH), 6.74-6.92(m, 4H, ArH), 6.95-7.22(dd, 4H, ArH, *J*=6.9).
4b	2.76-2.81(m, 2H, $ArCH_2$), 3.07-3.35(m, 4H, NCH_2CH_2), 3.75(s, 3H, OCH_3), 3.85(s, 6H, 2 x OCH_3), 3.88(s, 3H, OCH_3), 4.90(s, 1H, ArCHN), 5.63(br s, 1H, NH), 6.39(s, 1H, ArH), 6.67(s, 1H, ArH), 6.78-7.24(m, 5H, ArH), 7.35(m, 3H, ArH).
4c	2.66-2.72(m, 2H, $ArCH_2$), 2.92-3.40(m, 4H, NCH_2CH_2), 3.82(s, 3H, OCH_3), 3.84(s, 6H, 2 x OCH_3), 3.87(s, 3H, OCH_3), 4.97(m, 1H, ArCHN), 5.63 (br s, 1H, NH), 6.54(s, 1H, ArH), 6.65(s, 1H, ArH), 6.73(s, 1H, ArH), 6.80-7.22(m, 5H, ArH).
4d	2.28-2.53(m, 2H, $ArCH_2$), 2.88-3.25(m, 4H, NCH_2CH_2), 3.80(s, 3H, OCH_3), 3.84(s, 6H, 2 x OCH_3), 3.86(s, 3H, OCH_3), 4.90(m, 1H, ArCHN), 5.69 (br s, 1H, NH), 6.25(s, 1H, ArH), 6.41-6.73(m, 7H, ArH), 6.81-7.14(m, 1H, ArH).
4e	2.66-2.71(m, 2H, $ArCH_2$), 2.93-3.39(m, 4H, NCH_2CH_2), 3.81(s, 3H, OCH_3), 3.85(s, 6H, 2 x OCH_3), 3.87(s, 3H, OCH_3), 4.98(m, 1H, ArCHN), 5.61 (br s, 1H, NH), 6.52(s, 1H, ArH), 6.65(s, 1H, ArH), 6.74-6.87(m, 3H, ArH), 6.88-7.15(dd, 4H, ArH, *J*=8.4).
4f	2.66-2.71(m, 2H, $ArCH_2$), 2.93-3.39(m, 4H, NCH_2CH_2), 3.81(s, 3H, OCH_3), 3.85(s, 6H, 2 x OCH_3), 3.87(s, 3H, OCH_3), 4.98(m, 1H, ArCHN), 5.61 (br s, 1H, NH), 6.52(s, 1H, ArH), 6.65(s, 1H, ArH), 6.74-6.87(m, 3H, ArH), 6.88-7.15(dd, 4H, ArH, *J*=8.4).
4g	2.61-2.66(m, 2H, $ArCH_2$), 2.89-3.44(m, 4H, NCH_2CH_2), 3.75(s, 3H, OCH_3), 3.80(s, 6H, 2 x OCH_3), 3.87(s, 3H, OCH_3), 5.17(m, 1H, ArCHN), 5.51 (br s, 1H, NH), 6.41(s, 1H, ArH), 6.65(s, 1H, ArH), 6.45-7.05(m, 6H, ArH), 7.08(m, 1H,ArH).
4h	2.66-2.73(m, 2H, $ArCH_2$), 2.90-3.44(m, 4H, NCH_2CH_2), 3.76(s, 3H, OCH_3), 3.82(s, 6H, 2 x OCH_3), 3.87(s, 3H, OCH_3), 5.06(m, 1H, ArCHN), 6.04 (br s, 1H, NH), 6.42(s, 1H, ArH), 6.46-6.86(m, 6H, ArH), 7.85(m, 1H, ArH).
4i	2.28(s, 3H, CH_3) 2.76-2.81(m, 2H, $ArCH_2$), 3.08-3.36(m, 4H, NCH_2CH_2), 3.75(s, 3H, OCH_3), 3.84(s, 6H, 2 x OCH_3), 3.88(s, 3H, OCH_3), 5.60(m, 1H, ArCHN), 6.38 (br s, 1H, NH), 6.66(s, 1H, ArH), 6.77-7.04(m, 6H, ArH), 7.06(m, 2H, ArH).
4j	2.84-2.86(m, 2H, $ArCH_2$), 2.94-3.46(m, 4H, NCH_2CH_2), 3.62(s, 3H, OCH_3), 3.79(s, 6H, 2 x OCH_3), 3.83(s, 3H, OCH_3), 3.86(s, 3H, OCH_3), 5.75(m, 1H, ArCHN), 6.17(br s, 1H, NH), 6.60-6.65(m, 3H, ArH), 6.73-7.09(m, 5H, ArH), 7.91(br s, 1H, ArH).
4k	2.68-2.73(m, 2H, $ArCH_2$), 2.93-3.38(m, 4H, NCH_2CH_2), 3.77(s, 3H, OCH_3), 3.81(s, 6H, 2 x OCH_3), 3.85(s, 3H, OCH_3), 4.93(m, 1H, ArCHN), 5.66 (br s, 1H, NH), 6.65(m, 3H, ArH), 6.88(m, 2H, ArH), 7.11(s, 1H, ArH), 7.22(m, 2H, ArH).

Table 2. Continued

5a	2.33-2.51(m, 2H, $ArCH_2$), 2.95-3.50(m, 4H, NCH_2CH_2), 3.70(s, 3H, OCH_3), 3.81(s, 6H, 2 x OCH_3), 3.85(s, 3H, OCH_3), 5.75(br s, 1H, ArCHN), 6.09 (br s, 1H, NH), 6.56-7.00(m, 5H, ArH), 7.30-7.81(m, 7H, ArH).
5b	2.76-2.81(m, 2H, $ArCH_2$), 3.06-3.70(m, 4H, NCH_2CH_2), 3.81(s, 3H, OCH_3), 3.85(s, 6H, 2 x OCH_3), 3.88(s, 3H, OCH_3), 5.90(br s, 1H, ArCHN), 6.29 (br s, 1H, NH), 6.66-7.08(m, 5H, ArH), 7.33-7.83(m,7H,ArH)

The inhibition contraction was measured simply as percentage reduction in the height of spontaneous contractions. The percentage relaxation of all derivatives is compared in Table 3. The results are expressed as mean ± S.E. The statistical significance was treated with the paired student's t-test. P value < 0.01 were considered to be significant. Increase or decrease in tension was expressed as percent of maximal response to papaverine.

Table 3. Antispasmodic activity of compounds **4a-4k** and **5a-5b**

Compound	% Relaxation at various concentrations (μM, 500μL) 150 100 50 10			
Papaverine	68.46±3.49	43.90±2.72	26.70±0.32	7.80±0.27
4a	55.50±2.12*	38.10±0.54*	20.80±1.17*	15.00±1.16*
4b	56.29±3.30	38.45±1.48	22.10±1.95	10.45±0.86
4c	68.76±6.23	51.30±0.59	24.00±0.35	12.80±0.27
4d	64.89±3.73	50.17±1.60	20.80±1.82	10.75±0.45
4e	65.79±4.27	42.56±2.85	22.90±1.25	8.10±0.95
4f	85.46±3.25*	65.29±2.15*	44.86±3.90*	19.89±1.13*
4g	79.48±1.59*	60.21±3.20*	40.42±2.27*	15.15±1.01*
4h	69.35±2.27	42.17±3.39	26.25±1.33	9.95±0.58
4i	27.50±1.41*	14.50±0.50*	4.50±0.50*	1.20±0.20*
4j	35.29±2.29*	19.62±0.75*	10.28±0.85*	8.05±0.39*
4k	65.00±1.76	44.80±0.54	25.50±1.24	7.80±0.98
5a	20.54±2.10*	11.58±1.40*	1.50±0.50*	1.00±0.10*
5b	19.54±1.85*	12.50±1.44*	1.65±0.25*	1.20±0.20*

Values are mean ± S.E.M.

* P < 0.01, compared to papaverine

Structure activity relationship

The aromatic proton substitution by electron releasing alkyl groups on the phenyl ring in compound **4i** and **4j** showed decrease in antispasmodic properties in comparison to papaverine. Compounds with unsubstituted phenyl ring as in compound **4a** and **4b** showed significant

increase in antispasmodic activities in comparison to compound **4i** and **4j**. Comparable activities corresponding to papaverine were observed by all compounds containing halogen substitution on the phenyl ring **4c**, **4d**, **4e** and **4k**. However, dihalogen substitution in the phenyl ring compounds **4f** and **4g** with ortho and para positions showed significantly enhanced antispasmodic activities in comparison to papaverine. No appreciable change in the antispasmodic activities were observed by altering oxygen to sulphur in the amide moieties of the molecule.

Experimental Section

General Procedures. Melting points are recorded in open capillary tubes on Büchi melting point B-540 instrument and are uncorrected. Solvent system used throughout the experimental work for running TLC plates was ethylacetate – hexane. The ^{1}H NMR spectra were recorded in $CDCl_3$ as solvent (using TMS as internal standard) on a Bruker Avance Spectrospin 300 instrument at 300MHz. Mass spectra were run on a MALDI Kratos Analytical Kompact SEQ mass spectrometer using α-cyano-4-hydroxycinnamic acid (4-HCCA) as matrix under positive linear reflectance mode. IR spectra were recorded using KBr discs on a Shimadzu FTIR-8300 spectrophotometer.

General procedure. Synthesis of 1-(3,4-dimethoxybenzyl)-2-(arylcarbamoyl/ thiocarbamoyl)-6,7-dimethoxy -1,2,3,4-tetrahydroisoquinolines

1-(3,4-dimethoxybenzyl)-2-(4-chlorophenylcarbamoyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline (4e). A solution of *p*-chlorophenyl isocyanate (1.2 mmole) in dry acetonitrile (5 mL) was added slowly to a solution of tetrahydropapaverine 3 (1 mmole) in dry acetonitrile (5 mL). The mixture was stirred at room temperature for 2 h. After the completion (tlc) of the reaction, evaporated off the solvent, diluted the residue with water (25 mL) and extracted with ethylacetate (2x50 mL). The collective organic portion was washed with brine and dried (Na_2SO_4). It was finally concentrated and chromatographed on silica gel using ethylacetate – hexane as eluent. A final recrystallization from ethylacetate–hexane (15:85) affords pure **4e** (87%, mp 108-109 ^oC). The physical and spectral data of compounds are given in Table 1 and Table 2.

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