

JOSE LLOREDA CAMACHO & CO.

ABOGADOS

Calle 72 No. 5-83 Piso 5, Bogotá, D.C. Tel: 6069700 Fax 6069701

Señor

SUPERINTENDENTE DE INDUSTRIA Y COM
DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-077061- -00005-0000

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Act 523 RESPUESTA Folios: 8

Re: PI.-F.HOFFMANN-LA ROCHE AG.-Solicitud de Patente de
Invencción en Fase Nacional PCT para "FENIL METANONAS
SUSTITUIDAS POR HETEROCÍCLICO COMO INHIBIDORES
DEL TRANSPORTADOR 1 DE GLICINA".-Clase C07D 209/44.-
Expediente número 07-077.061-

1. Me refiero al auto dictado por ese Despacho notificado mediante fijación en lista de 11 de Febrero de 2011.

2. De acuerdo con el Concepto Técnico No. **447** se tiene que:

"Como consecuencia de la búsqueda de anterioridades de materia relacionada con la de la presente solicitud, se determinó que existe en el estado de la técnica el siguiente documento que eventualmente afectaría los requisitos de patentabilidad de esta solicitud:

- 1- EGYPTIAN JOURNAL OF PHARMACOLOGICAL SCIENCES, Vol. 29, No. 1-4, 1988, pags 545-551, título: "Synthesis of certain 6-nitro and 6-chloroindazole derivatives", autor: EL-GHANDOUR ET AL.

3. Para responder a los requerimientos del señor Examinador de conformidad con el Artículo 46 de la Decisión Andina 486 de 2000, anexo me permito presentar a ese Despacho copia del siguiente documento solicitado:

- 1- EGYPTIAN JOURNAL OF PHARMACOLOGICAL SCIENCES, Vol. 29, No. 1-4, 1988, pags 545-551, título: "Synthesis of certain 6-nitro and 6-chloroindazole derivatives", autor: EL-GHANDOUR ET AL.

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4. En vista de lo anterior, ruego a usted tomar atenta nota y proceder de conformidad.

Señor Superintendente,



ALICIA LLORED A RICAURTE

T.P. 53.215

XP008062926

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Egypt. J. Pharm. Sci. Vol. 29, No. 1-4, pp. 545-551 (1988)**Synthesis of Certain 6-Nitro and 6-Chloroindazole Derivatives****A.M. El-Ghandour, M.M. Badran, K.M. Ghoneim
and M. Khalifa***Organic Chemistry Department, Faculty of Pharmacy,
Cairo University, Egypt.*

6-NITROINDAZOLE was obtained by nitration of o-toluidine in a strong acid medium followed by diazotisation of the nitro amine then cyclization of the so obtained diazonium salt via an internal nucleophilic attack. On the other hand, the 6-chloro derivative was prepared by the acylation of 4-chloro-o-toluidine, nitrosation of the acylated amine and subsequent cyclization. Reacting equimolar amounts of the nitro or the haloindazole in dry benzene with a number of acid chlorides yielded the corresponding N-acyl derivatives (II), while compounds having the general formula III were prepared by condensing the nitro or the haloheterocycle with aryl sulphonyl chlorides in dry benzene as solvent using triethylamine as the acid binding agent. Moreover, a comparison was held regarding the reactivity of the substrates (the nitro and the haloheterocycles) as well as the reactivity of the acylating agents (aroyl chlorides and aryl sulphonyl chlorides).

Indazoles as a class of biologically active molecules have been shown to have diverse activity as bactericidal, fungicidal, herbicidal and pesticidal agents⁽¹⁻⁴⁾.

The above findings stimulated the interest in suggesting and synthesising certain nitro and chloroindazoles, having in common the substituent on position 6 in the hope that the new derivatives may show superior biological activity* than the parent heterocycle.

Synthesis of Intermediates Target Compounds and Discussion :

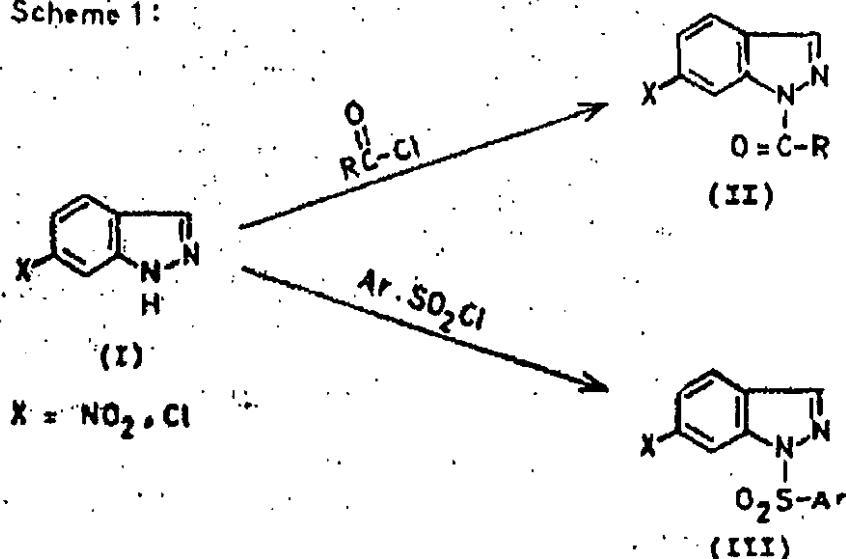
The starting materials and likewise the acylating agents were prepared according to reported procedures⁽⁵⁾. The nitroindazole (I, X = NO₂) was obtained by nitration of o-toluidine in a strong acid medium followed by diazotization of the nitro amine, then

* Target compounds are under preliminary pharmacological screening as antimicrobial agents.

cyclization of the so obtained diazonium salt via an internal nucleophilic attack. On the other hand, the β -chloro derivative (I, $X = Cl$) was prepared by the acylation of 4-chloro-toluidine, nitrosation of the acylated amine and subsequent cyclization⁽⁹⁾.

The target N-acyl (II) and N-aryl sulphonyl (III) derivatives of 6-nitro and 6-chloroindazoles were prepared by heating under reflux equimolar amounts of the nitro or the haloheterocycle with the respective acyl or aryl sulphonyl chloride in dry benzene using triethylamine as the acid binding agent (Scheme 1). The reaction time varied from 7-24 hr according to the substrate and the acylating or aryl sulphonating agent.

Scheme 1:



Thus, reaction with 6-nitroindazole, required less time than the corresponding chloro derivative. The greater reactivity of the former may be attributed to the powerful electron withdrawing nitro group which acts by -I and -M effects.

On the other hand, the reactivity of the acid chlorides varies with the nature of the substituent on the nucleus, whether electron withdrawing or electron releasing. Thus, as expected, with the nitro substituted acid chlorides, less time was needed for complete reaction with the parent indazole derivative than that with the less reactive alkoxy substituted ones.

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Likewise, comparison of the reactivity of the carbonyl chlorides and their sulphur analogues revealed that carbonyl chlorides are more reactive than the corresponding aryl sulphonyl chlorides as shown from the reaction time (Tables 1-4).

This observation is feasible in the light of what has been reported⁽¹⁾ that the reactivity of acyl chlorides may be attributed to the ease with which the electrophilic centre is attacked. The ease with which the carbonyl carbon atom forms a bond with the attacking nucleophile, with sp^2 to sp^3 change in hybridization, compared with the relative difficulty with which the sulphur of the sulphonyl chloride (already sp^3) accepts the nucleophile and thereby undergoing expansion of its octet to less stable d-orbital.

The structure of the above series (II) and (III) was confirmed by elemental analysis and IR spectral data. Thus, all the nitro and the halo indazole derivatives (II and III) showed no absorption in the 3500-3200 cm^{-1} region, indicating the absence of -NH group originally present in the parent substrates (I). While compounds type II showed strong absorption bands at 1730-1700 cm^{-1} assignable to the stretching frequency of the acyl carbonyl group.

Experimental

Melting points were determined in open capillary tube apparatus and are uncorrected. Elemental micro-analyses were performed by the Microanalytical Unit, Faculty of Science, Cairo University, A.R. Egypt. IR spectra were determined on a Beckmann IR-20 and a Spektromom 2000 using nujol mulls.

6-Nitroindazole (I, X = NO₂) :

It was prepared using a reported procedure⁽²⁾.

6-Chloroindazole (I, X = Cl) :

It was prepared using a reported procedure⁽³⁾.

N-Acyl-6-nitroindazoles (IIa-k, X NO₂) :

A mixture of 6-nitroindazole (0.002 mole) and the acid chloride (0.002 mole) in dry benzene (30 ml) was heated at reflux for 9-16 hr (according to acylating agent). The reaction mixture was filtered while hot, concentrated under reduced pressure to nearly dryness and the residue crystallized from the appropriate solvent (Table 1).

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TABLE 1. N-Acyl-6-Nitroindazoles.

No.	R	Reflux time (hours)	Solvent of crystallization	Yield %	m.p. °C	Formula	Analysis %	
							Calcd	Found
II _a	-CH(C ₆ H ₅) ₂	13	pet. ether (60-80°)	68	135	C ₂₁ H ₁₅ N ₃ O ₃	C 70.6 H 4.2 N 11.8	70.6 4.2 11.9
II _b	-3,5(NO ₂) ₂ C ₆ H ₃	9	acetone	76	738	C ₁₄ H ₇ N ₃ O ₇	C 47.1 H 2.0 N 19.6	47.1 2.6 20.0
II _c	-2(Cl)C ₆ H ₄	8	methanol	82	172	C ₁₄ H ₈ ClN ₃ O ₃	C 55.8 H 2.6 N 13.9 Cl 11.8	55.4 2.5 14.0 11.8
II _d	-4(Cl)C ₆ H ₄	11	benzene	85	205	C ₁₄ H ₈ ClN ₃ O ₃	C 55.8 H 2.6 N 13.9 Cl 11.8	55.6 2.5 14.1 10.3
II _e	-4(Br)C ₆ H ₄	11	benzene	79	203	C ₁₄ H ₈ BrN ₃ O ₃	C 48.6 H 2.3 N 12.1 Br 23.1	48.8 2.4 12.1 23.1
II _f	-C ₁₀ H ₇	12	benzene	81	204	C ₁₉ H ₁₁ N ₃ O ₃	C 68.3 H 3.5 N 13.3	68.5 3.5 13.2
II _g	-3(Cl)C ₆ H ₄	10	benzene	72	170	C ₁₄ H ₈ ClN ₃ O ₃	C 55.8 H 2.7 N 14.0 Cl 11.8	55.9 3.0 14.0 11.9
II _h	-2(NO ₂)CH=CHC ₆ H ₄	9	benzene	77	200	C ₁₆ H ₁₀ N ₃ O ₅	C 56.8 H 3.0 N 16.6	56.8 3.2 16.5
II _i	-2,5(OH)(NO ₂)C ₆ H ₃	10	benzene	63	210	C ₁₄ H ₈ N ₃ O ₆	C 51.2 H 2.4 N 17.1	51.4 2.7 17.6
II _j	-3,4,5(OCH ₃) ₃ C ₆ H ₃	14	benzene	78	195	C ₁₇ H ₁₅ N ₃ O ₆	C 57.1 H 4.2 N 11.8	56.6 3.9 12.0
II _k	-4(NO ₂)C ₆ H ₃	16	pet. ether (60-80°)	58	170	C ₁₅ H ₁₁ N ₃ O ₄	C 60.6 H 3.7 N 14.1	60.4 4.2 13.7

N-Acyl-6-chloroindazoles (IIa-f, X = Cl) :

A mixture of 6-chloroindazole (0.002 mole) and the acid chloride (0.002 mole) in dry benzene (40 ml) containing few drops of triethylamine was heated at reflux for 7-15 hr (according to the acylating agent). The reaction mixture was cooled and filtered from suspended inorganic salt. The filtrate was concentrated under reduced pressure and the residue crystallized from the appropriate solvent (Table 2).

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TABLE 2. N-Acyl-6-Chloroindazole.

No.	R	Reflux time (hours)	Solvent of crystallisation	Yield %	m.p. °C	Formula	Analysis %	
							Calcd	Found
II _a	-C ₆ H ₅ ^(*)	-	methanol	88	123	C ₁₄ H ₉ ClN ₂ O	C 65.4 H 3.5 Cl 14.0	65.7 3.7 13.9
II _b	-4(NO ₂)C ₆ H ₄	7	ethanol	71	175	C ₁₄ H ₈ ClN ₂ O ₃	C 55.8 H 2.7 N 14.0 Cl 11.8	56.0 3.1 13.8 11.8
II _c	-2(Cl)C ₆ H ₄	11	benzene	76	130	C ₁₄ H ₈ Cl ₂ N ₂ O	C 57.9 H 2.8 Cl 24.1	58.2 3.0 24.1
II _d	-4(Or)C ₆ H ₄	14	benzene/ pet. ether (60-80°)	69	171	C ₁₄ H ₈ BrClN ₂ O	C 50.0 H 2.4 Cl 10.4	50.5 2.9 10.6
II _e	-C ₁₀ H ₇	25	benzene	82	188	C ₁₈ H ₁₁ ClN ₂ O	C 70.4 H 3.6 N 9.1 Cl 13.7	70.8 3.2 9.2 12.1
II _f	-2(NO ₂)CH-CHC ₆ H ₄	11	benzene	83	178	C ₁₆ H ₁₀ ClN ₂ O ₃	C 58.5 H 3.0 N 12.8 Cl 11.0	58.5 3.3 13.2 11.3

(*) was prepared by Schotten-Baumann's conditions.

N-Arylsulphonyl-6-nitroindazoles (IIa-d, X = NO₂) :

A mixture of 6-nitroindazole (0.002 mole) and the sulphonyl chloride (0.02 mole) in dry, benzene (40 ml) in presence of few drops of triethylamine was heated at reflux for 13-22 hr (according to sulphonating agent). The reaction mixture was filtered and either cooled or concentrated to a small bulk under reduced pressure. The product was then crystallised from the appropriate solvent (Table 3).

N-Arylsulphonyl-6-chloroindazoles (IIa-d, X = Cl) :

A mixture of 6-chloroindazole (0.002) and the sulphonyl chloride (0.002 mole) in dry benzene (50 ml) in presence of few drops of triethylamine was heated at reflux for 16-24 hr (according to sulphonating agent). The reaction mixture was cooled, filtered and the filtrate concentrated under reduced pressure. The residue was crystallised from the appropriate solvent (Table 4).

TABLE 3. N-Arylsulphonyl-6-Nitroindazoles.

No.	Ar	Reflux time (hours)	Solvent of crystallization	Yield %	m.p. °C	Formula	Analysis %	
							Calcd	Found
III _a	-C ₆ H ₅	20	benzene/ pet. ether (60-80°)	81	172	C ₁₃ H ₉ N ₃ SO ₄	C 51.5 H 3.0 N 13.9 S 10.6	51.6 3.2 14.2 10.4
III _b	-4(Cl)C ₆ H ₄	14	benzene/ pet. ether (60-80°)	62	171	C ₁₃ H ₈ ClN ₃ SO ₄	H 12.5 S 9.5 Cl 10.5	12.5 9.4 10.8
III _c	-3(NO ₂)C ₆ H ₄	13	benzene/ pet. ether (60-80°)	71	165	C ₁₃ H ₈ N ₄ SO ₆	C 44.8 H 2.6 S 9.2	44.8 3.0 9.6
III _d	-4(NH-C(=O)-CH ₃) C ₆ H ₄	22	acetone/ ethanol	65	150	C ₁₅ H ₁₂ N ₄ SO ₅	C 50.0 H 3.3 N 15.6 S 8.9	50.1 3.6 15.2 9.2

TABLE 4. N-Arylsulphonyl-6-Chloroindazoles.

No.	Ar	Reflux time (hours)	Solvent of crystallization	Yield %	m.p. °C	Formula	Analysis %	
							Calcd	Found
III _a	-C ₆ H ₅	22	benzene	79	146	C ₁₃ H ₉ ClN ₂ SO ₂	C 53.2 H 3.1 S 10.9	53.4 3.1 10.7
III _b	-4(Cl)C ₆ H ₄	16	pet. ether (60-80°)	72	125	C ₁₃ H ₈ ClN ₂ SO ₂	C 46.7 H 2.4 N 8.6 Cl 21.7	49.0 2.8 8.7 22.0
III _c	-3(NO ₂)C ₆ H ₄	16	benzene	69	135	C ₁₃ H ₈ ClN ₃ SO ₄	C 46.2 H 2.4 S 9.5	46.5 2.8 9.0
III _d	-4(CH ₃)C ₆ H ₄	24	ethanol	60	130	C ₁₅ H ₁₁ ClN ₂ SO ₂	Cl 11.7 H 9.1 S 10.4	11.3 9.5 10.3

References

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تشييد مشتقات معينة من ال-٦-نيترو و ٦ - كلورواندازول

اسماء القندور ، مهجة بدران ، خديجة منصور طليم ومنصور خليطه
قسم الكيمياء النظرية - كلية الصيدلة - جامعة القاهرة

تتضمن النيترو والوالموجبتات الاندازول (I) مع العديد من كلوريدات الاحماض في وجود البنزين المطري الجاف لتعطي مشتقات ذات التركيب البنائي (II) بينما يمكن الحصول على المركبات التي لها التركيب البنائي (III) يتفاعل النيترو او الهالواندازول (1) مع اول سلفونيل الكلوريدات في وجود البنزين المطري الجاف .

وتد عتد دراسة مقارنة بين عوامل الاسئلة المستخدمة (دى الاربيل' كلوريد والاربيل سلفونيل الكلوريد) .

Egypt. J. Pharm. Sci., 29, No. 1-4 (1988)

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