LLOREDA & CIA. S. A.
ABOGADOS

BOGOTA - COLOMBIA
OFICINA FUNDADA EN 1941
APARTADO AEREO 12304
TEL: 57-1-3264270 57-1-6069700
FAX: 57-1-3264271 57-1-6069701
CABLES: LLOREDA
CALLE 72 No. 5-83 5°. PISO
www.lloredacamacho.com
jllcco@lloredacamacho.com

246

246

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: P1.-**ASTRAZENECA AB.**-Solicitud de Patente de Invención en Fase Nacional PCT para **"INDOLES SUSTITUIDOS NOVEDOSOS"**.-Clase **C07D 209/30**.-Expediente número **04-120.052**.-

1. Me refiero al auto dictado por ese Despacho notificado mediante fijación en lista de 11 de Abril de 2008.

2. De acuerdo con el Concepto Técnico No. **734** se tiene que:

"Como consecuencia de la búsqueda de anterioridades de materia relacionada con la presente invención, se determinó que existen en el estado de la técnica los siguientes documentos que eventualmente afectarían los requisitos de patentabilidad de esta solicitud:

- **Tetrahedron Letters, vol. 26, No. 15, 1985, Josefina García et al: "A novel synthesis of 3-cyanoindoles and a new route to indole-3-carboxylic acid derivatives", page 1827-page 1830, RN 98508-73-7; y**

- **STN International, file CAPLUS, CAPLUS accession no. 1977: 535057, Document No. 87:135057, Sankyo Co., Ltd.: "3-Indolyl-thio ethers"; & JP, A2 52039671, 19770328, RN 64137-76-4, 54491-43-9, 56366-45-1.**

3. Para responder a los requerimientos del señor Examinador de conformidad con el Artículo 46 de la Decisión 486, anexo me permito presentar a ese Despacho copia de los siguientes documentos solicitados:

247

* Tetrahedron Letters, vol. 26, No. 15, 1985, Josefina García et al: "A novel synthesis of 3-cyanoindoles and a new route to indole-3-carboxylic acid derivatives", page 1827-page 1830, RN 98508-73-7; y

247

* STN International, file CAPLUS, CAPLUS accession no. 1977: 535057, Document no. 87:135057, Sankyo Co., Ltd.: "3-Indolyl-thio ethers"; & JP, A2 52039671, 19770328, RN 64137-76-4, 54491-43-9, 56366-45-1.

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

Señor Superintendente,

ALICIA LLOREDA RICAURTE

T.P. 53.215

Tetrahedron Letters,Vol.26,No.15,pp 1827-1830,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

A NOVEL SYNTHESIS OF 3-CYANOINDOLES AND A NEW ROUTE TO INDOLE-3-CARBOXYLIC ACID DERIVATIVES[1].

Josefina Garcia,[a] Robert Greenhouse,[a]
Joseph M. Muchowski[b]* and Jose Antonio Ruiz[a]

a) Syntex, S.A., División de Investigación, Apartado Postal 10-820, 11000 México, D.F. b) Syntex Research, Institute of Organic Chemistry, 3401 Hillview Ave., Palo Alto, California 94304

SUMMARY: 2-Alkyl-3-cyanoindoles are obtained when 1-alkylmethyl-2-chloro-(or 2-phenylsulfonyl)-3-phenylsulfonylindoles are reacted with excess azide ion (90°/DMF). The reaction is considered to occur by a fragmentation recombination process in which the Schiff's base 12 is of central importance. This proposal is supported by the formation of 2-substituted indole-3-carboxylates 17 from aldehydes and the α-phenylsulfonyl-o-aminophenylacetic acid ester derivative 16.

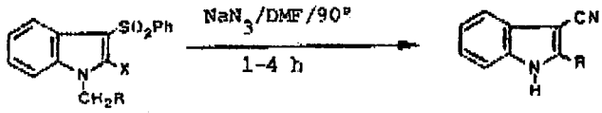
Although 2-chloro-3-acylindoles are relatively readily available[2], the nucleophilic substitution reactions of these compounds have hardly[3] been investigated. A facile synthesis of the electronically related 2-chloro-3-phenylsulfonylindoles (6) was recently devised in these laboratories and the susceptibility thereof to nucleophiles was examined. This report summarizes the results of the study with particular emphasis on the unique reaction which takes place between 6 and azide ion.

The 2-chloro-3-phenylsulfonylindoles were prepared most efficaciously by the routes shown in Scheme I. Thus, 3-phenylsulfenylindole (1)[4] was oxidized with 1 equiv. of m-chloroperoxybenzoic acid (MCPBA) to the sulfoxide 2[5], which was alkylated on nitrogen with various alkyl halides (e.g., $PhCH_2Br$, $BrCH_2CO_2Et$) in DMF solution containing sodium hydride. The conversion of the 1-alkyl-3-phenylsulfinylindoles (3) into the corresponding 2-chloro-3-phenylsulfenyl compounds 5 was effected with thionyl chloride (0°/$NaHCO_3$). This notably efficient process (80-95% yields), for which close analogies are known in non-aromatic systems[6,7], is considered to proceed via the sulfonium salt 4[8]. Oxidation of the chlorosulfides 5 with a slight excess of MCPBA (0°/CH_2Cl_2) gave the required chlorosulfones 6. These compounds could also be prepared by a reaction sequence wherein 3-phenylsulfinylindole was first converted into 2-chloro-3-phenylsulfenylindole (7), which was subsequently oxidized to the sulfone 8 and then N-alkylated ($ClCH_2CN$; $PhCOCH_2Br$).

Whereas the reaction of 1-benzyl-2-chloro-3-phenylsulfonylindole (6, R = Ph) with nucleophiles such as diethyl sodiomalonate, sodium phenolates, sodium thiolates and primary amines gave the expected 2-substituted-3-phenylsulfonylindoles, the structure of the product obtained from 6 (R = Ph), and excess sodium azide (3 equiv./DMF) at 90°, was completely unanticipated. This substance, mp 240°, analysed for $C_{15}H_{10}N_2$, had a mass spectral molecular weight of 218

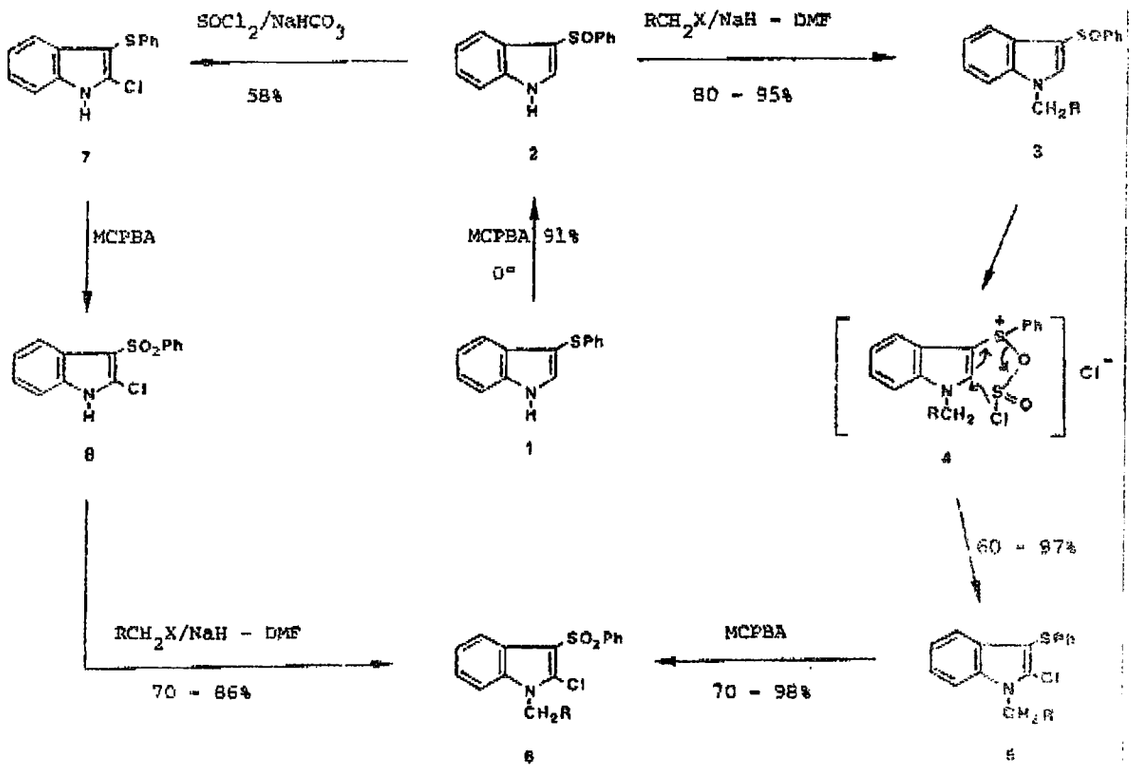
~~249~~ 249

Table. Synthesis of 2-Substituted-3-cyanoindoles

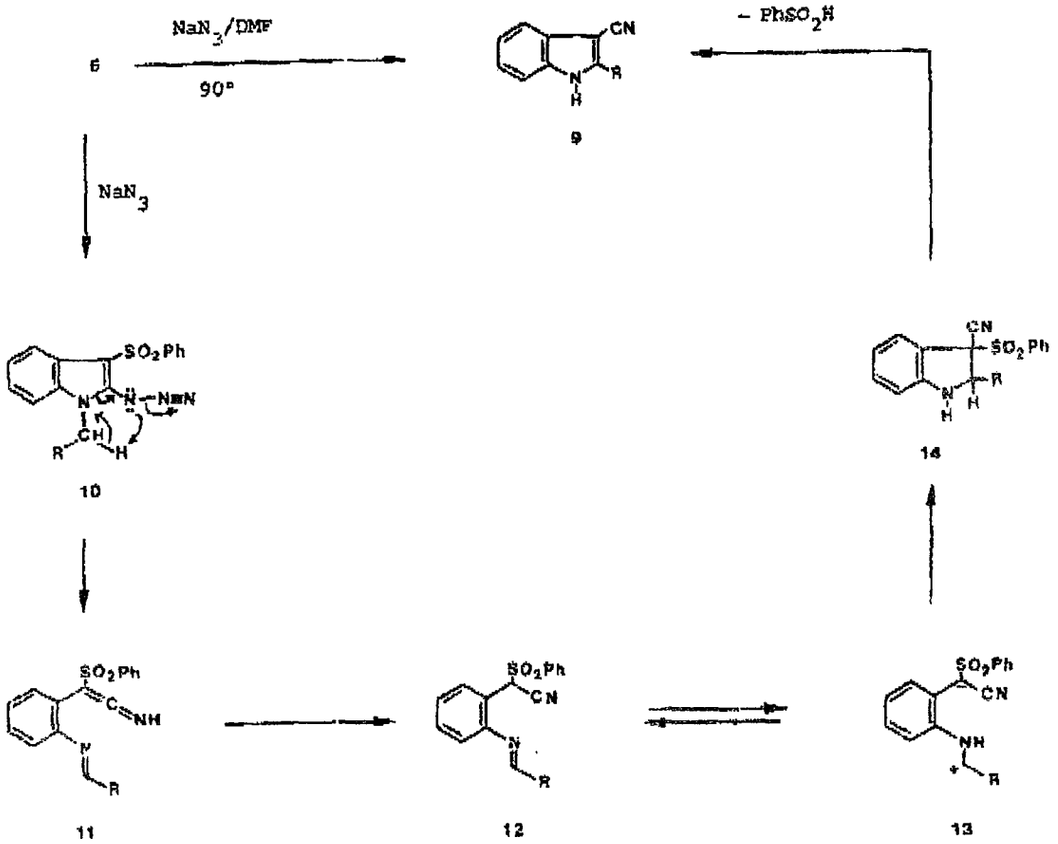


Entry	R	X	%[a]
1	Ph	Cl	99
2	Ph	SO_2Ph[b]	78
3	CH_3	SO_2Ph[b]	24
4	CO_2CH_3	Cl	84
5	CN	Cl	26
6	CN	SO_2Ph[b]	32
7	PhCO	Cl	59

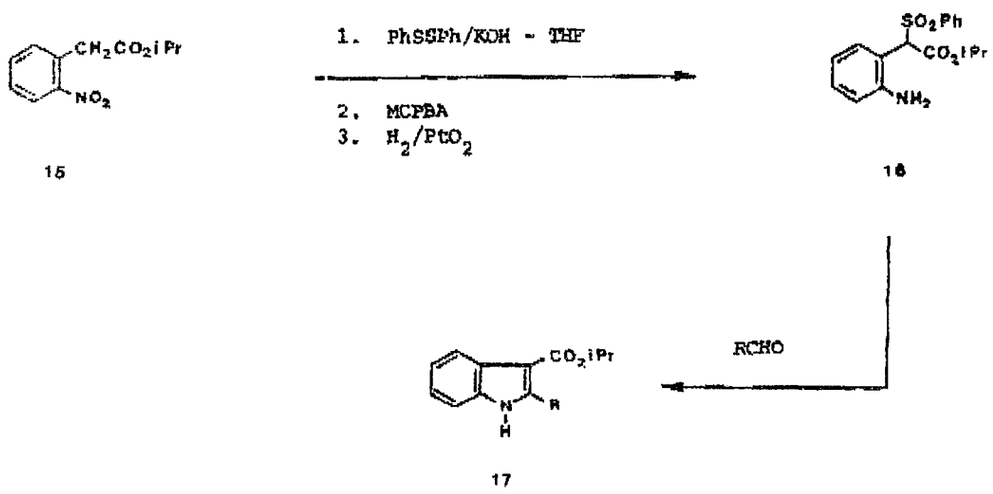
a) None of the reactions, except that of entry 1, was optimized.
b) These compounds were prepared by N-Alkylation of 2,3-bis-phenylsulfenylindole[4] followed by prolonged oxidation with MCPBA.



Scheme I



Scheme II



Scheme III

and strong IR bands at 3240 and 2195 cm^{-1}. The NMR spectrum showed absorptions only for aromatic hydrogens and one exchangeable proton. This data suggested that the product was either 2-phenyl-3-cyanoindole (9, R = H, Scheme II) or 2-cyano-3-phenylindole. The former was shown to be correct by direct comparison with an authentic sample synthesised from 2-phenylindole and chlorosulfonyl isocyanate[9].

The formation of 2-alkyl-3-cyanoindoles (9) from 1-alkylmethyl-2-chloro-3-phenylsulfonylindoles (6) does appear to have some generality as judged from the examples listed in the Table. Furthermore, the leaving group at C-2 need not be chloride ion since 1-alkylmethyl-2,3-bis-benzenesulfonylindoles (entries 2,3,7) yield the same products with azide ion. With regard to the mechanism of this remarkable reaction, it is noteworthy that 9(R = Ph) is slowly formed from 6(R = Ph), even at room temperature, and at no time is the azido compound 10 observed. It is therefore suggested that the transformation proceeds by simultaneous loss of nitrogen and fragmentation of the, presumably unstable, azide 10 to the imino ketenimine 11. The tautomeric α-phenylsulfonylnitrile 12, or the 1,5-dipole 13 corresponding thereto, would be expected to cyclize to 14, as in the syntheses of indolines (and indoles) recently described by Speckamp[10] and Grigg[11], and the loss of benzenesulfinic acid from 14 would complete the process. The feasibility of the latter stages of this process was examined as follows. The i-propyl ester of o-nitrophenylacetic acid 15 (Scheme III) was reacted sequentially with diphenyldisulfide (KOH powder/THF), excess MCPBA and hydrogen (PtO_2/50 psig). Brief heating of the resulting sensitive amino compound 16 with benzaldehyde (1 equiv.) in acetonitrile, at reflux temperature, gave i-propyl 2-phenylindole-3-carboxylate (17, R = Ph), mp 124° in 83% yield, identical to a sample synthesised from 2-phenyl-3-chlorocarbonylindole[12] and 2-propanol. Analogous products were obtained from n-decanal (57%) and cinnamaldehyde (76%). These results strongly support the suggested mechanistic sequence and demonstrate that 2-substituted-indole-3-carboxylic acid derivatives are readily available from o-nitrophenylacetic acid.

Acknowledgements: We thank Professor Gilbert Stork (Columbia University) and Dr. T.T. Li (Syva) for extensive discussions of the mechanistic aspects of this paper and Drs. M. Maddox and L. Tökes for invaluable assistance in the interpretation of the NMR and mass spectra of 9(R = Ph).

References and Notes:

1. Contribution no. 686 from the Syntex Institute of Organic Chemistry.
2. L. Marchetti and A. Andreani, Ann. Chim. (Rome), 63, 681 (1973); J. Bergman, R. Carlsson and B. Sjoberg, J. Heterocyclic Chem., 14, 1123 (1977), A. Andreani, D. Bonazzi, M.A. Guarnieri, F. Andreani, P. Strocchi and N. Montanaro, J. Med. Chem., 20, 1344 (1977).
3. R.S. Sagitullin, T.V. Mel'nikova, and A.N. Kost, USSR Patent 394,373 (1973); Chem. Abstr., 79, 146501 (1973).
4. K. Anzai, J. Heterocyclic Chem., 16, 567 (1979).
5. All new compounds gave satisfactory elemental analyses and were fully characterized by the usual spectroscopic methods.
6. G.A. Russell, E. Sabourin and G.J. Mikol, J. Org. Chem., 31, 2854 (1966); N. Miyamoto, D. Fukuoka, K. Utimoto and H. Nozaki, Bull. Chem. Soc. Japan, 47, 1817 (1974).
7. O. De Lucchi, G. Marchioro and G. Modena, J. Chem. Soc. Chem. Commun., 513 (1984).
8. Under similar conditions, 2-chloro-3-arylsulfonylpyrroles are obtained from 3-arylsulfinylpyrroles; J. Garcia and R. Greenhouse, Unpublished results.
9. G. Mehta, D.N. Dar, S.C. Suri, Synthesis, 374 (1978).
10. J. Dijink, J.N. Zonjee, B.S. de Jong and W. N. Speckamp, Heterocycles, 20, 1255 (1983).
11. R. Grigg and H.Q.N. Gunaratne, J. Chem. Soc. Chem. Commun., 661 (1984).
12. J. Bergman, R. Carlsson and B. Sjoberg, J. Heterocyclic Chem., 14, 1123 (1971).

(Received in USA 28 December 1984)

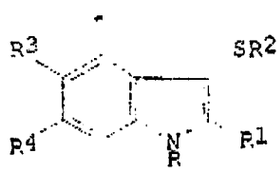
252

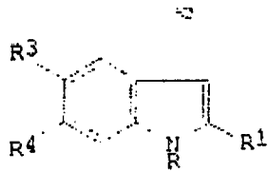
252

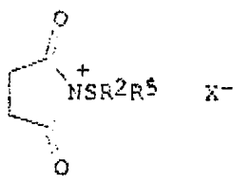
AN 1977:535057 CAPLUS
DN 87:135057
TI 3-Indolyl thio ethers
IN Tomita, Kuniyuki; Terada, Atsusuke; Tachikawa, Ryuji
PA Sankyo Co., Ltd., Japan
SO Japan. Kokai, 5 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
IC C07D209-30
CC 27-11 (Heterocyclic Compounds (One Hetero Atom))
FAN.CNT 1

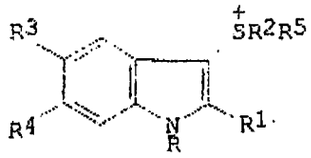
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 52039671	A2	19770328	JP 1975-114474	19750922

GI


I


II


III


IV

AB Eight title thio ethers I (R = H, Me; R1 = H, Me, Ph; R2 = Me, Et, Ph, CH2CO2H, CH2CO2Et; R3 = H, Cl, Me; R4 = H, MeO) were prepd. by reaction of indoles II with succinimidosulfonium halides III (R5 = alkyl, carboxyalkyl, etc.; X = halo) followed by thermal decompn. of the resulting IV. I had analgesic, antiinflammatory, and antipyretic activities (no data). Thus, 1.17 g indole was added to 2.23 g III (R2 = R5 = Et, X = Cl) in CHCl3 at -20°, the mixt. stirred 1 h at room temp., and the resulting crystals were heated 5 min at 130-40° under N to give 1.20 g I (R = R1 = R3 = R4 = H, R2 = Et).

ST indolyl thio ether; analgesic indolyl thio ether; antipyretic indolyl thio ether; antiinflammatory indolyl thio ether

IT Analgesics
Antipyretics
Inflammation inhibitors
(3-indolyl thio ethers)

IT 59321-25-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and thermal decompn. of)

IT 1484-16-8P 40015-10-9P 54466-90-9P 54491-43-9P 56366-45-1P 59321-38-9P 64137-76-4P 64137-77-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

IT 59741-18-3
RL: RCT (Reactant)
(reaction of, with indole)

IT 120-72-9, reactions
RL: RCT (Reactant)
(reaction of, with succinimidosulfonium chloride)