Synthesis of Indole Derivatives. Part III. Extension of the Amine Oxide Rearrangement (1).

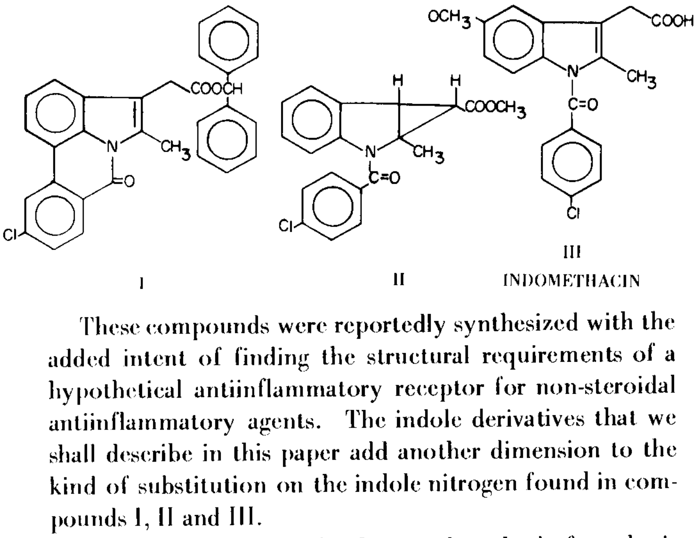
B. S. Thyagarajan and K. C. Majumdar*

Chemistry Department, University of Idaho, Moscow, Idaho 83843

Received May 28, 1974

The synthesis of *N,N*-bis(4-aryloxy-2-butynyl)anilines and their rearrangement to 1,2,3-trisubstituted indoles is described.

In recent publications (2,3) we have outlined a completely new synthetic route towards the synthesis of indole derivatives. This reaction appears to be of additional value in view of the recent interest in non-steroidal antiinflammatory compounds (I, II) related to indomethacin (III) (4,5).

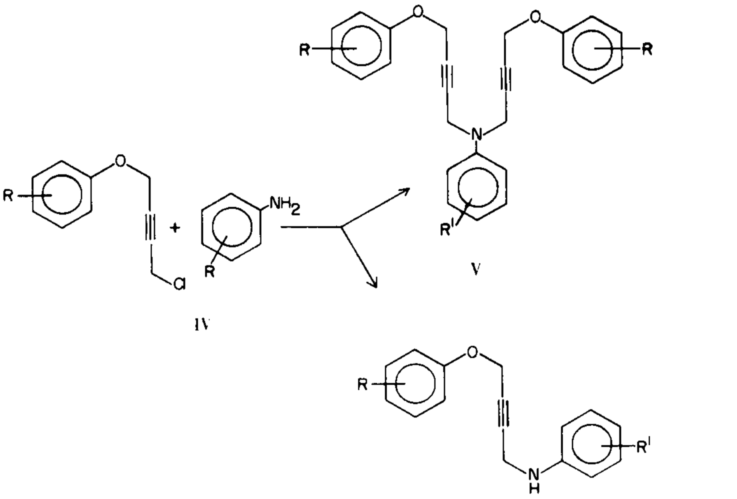


I II III INDOMETHACIN

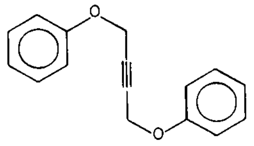
These compounds were reportedly synthesized with the added intent of finding the structural requirements of a hypothetical antiinflammatory receptor for non-steroidal antiinflammatory agents. The indole derivatives that we shall describe in this paper add another dimension to the kind of substitution on the indole nitrogen found in compounds I, II and III.

The starting materials for this novel method of synthesis of indoles were substituted anilines and an appropriate 1-aryloxy-4-chloro-2-butyne (IV). Simple nucleophilic substitution readily afforded in good yields the *N,N*-dialkylated amines (V). Monoalkylated anilines (VI) were also formed in some instances.

When an attempt was made to characterize the dialkylated amines (V) by way of their methiodides, the quaternary ammonium iodide that was isolated was not that of V but merely, trimethylanilinium iodide. The iodide ion liberated on methylation apparently effected a cleavage of the butynyl moiety (6). The 4-aryloxy-2-butynyl iodide that was thus formed was characterized by its facile conversion into known 1,4-diaryloxy-2-butyne (VII) (13). In

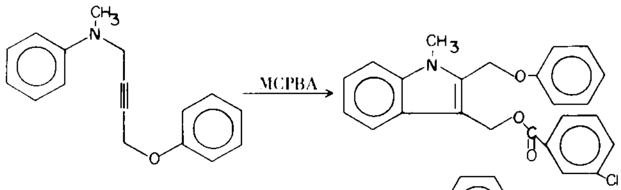


IV V VI

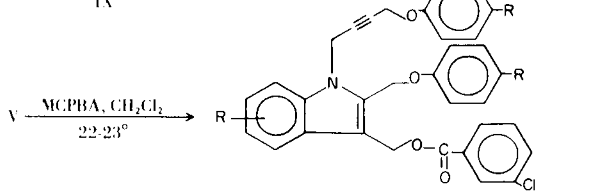


VII

view of this apparent instability towards quaternization, it was of interest to determine whether the propynyl amine moiety in V would indeed undergo the amine oxide rearrangement required to form the indoles (2). This question is especially intriguing in the light of the work of Padwa and Hamilton (7) who described the formation of stilbenes and stilbene oxides during the peracid treatment of triphenylaziridines. However, when the bis propynyl anilines (V) were reacted with meta chloroperbenzoic acid at ambient temperatures, indoles VIII were obtained in high yields. As in the case of the rearrangement of IX, the metachlorobenzoyl function appeared on the 3-methyl carbon while the other 4-aryloxy-2-butynyl moiety was appended on the indole nitrogen.



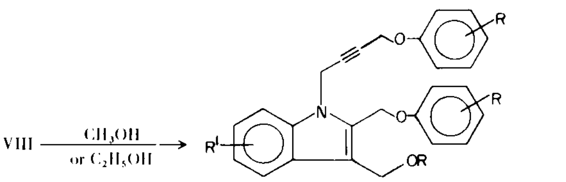
IX



VIII

This exceedingly facile and mild synthesis of indole derivatives establishes two more features. In the peracid induced rearrangement of propynyl anilines, the triple bond is completely unaffected unlike other acetylenes wherein meta chloroperbenzoic acid has been reported to form oxirenes as intermediates (8,9) and therefore not at all involved in the formation of the indole. This corroborates the mechanism proposed by us elsewhere (2) for this unusual rearrangement. And, secondly the instability of the dialkylated aniline V towards an iodide ion in rupture of the propynyl linkage is not extended to the reaction with the benzoate ion formed in situ during the amine oxide formation.

As in earlier studies (2,3), the indoles (VIII) were subjected to methanolysis and ethanolysis resulting in facile replacement of the benzoate group yielding X and XI. Thus, the reaction pattern is completely reproduced in compounds of the series V as in the anilines IX. In related studies concerning the hydration of 1,4-diaryloxy-2-buynes



X, R CH_3
XI, R C_2H_5

(10) we have shown the facile formation of chromenes under mecury ion catalysis. It was therefore of interest to investigate the possibilities of similar hydrations with the compounds of the type VIII. However, in the event, only a complex mixture of illdefined and inseparable products formed. Further work is in progress to investigate the hydration reaction in greater detail, as this would lead to indole derivatives closely resembling the indomethacin molecule. Several of the indoles obtained in this study are currently under pharmacological evaluation by the Warner-Lambert Research Institute.

EXPERIMENTAL

Melting points were obtained on a Thomas-Hoover Capillary melting point apparatus and were not corrected. Nuclear Magnetic Resonance (nmr) spectra were obtained with a Varian A-60 spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectral data were obtained on a Hitachi-Perkin-Elmer RMU-6E single focus low resolution instrument at 70 ev. Microanalyses were performed by Mr. David Harsch in this department.

Synthesis of 1-Aryloxy-4-chlorobut-2-yne.

These were synthesized according to our earlier published procedure (11). 1-(*p*-Methoxyphenoxy)-4-chlorobut-2-yne was synthesized in addition to 1-(*p*-chlorophenoxy)-4-chlorobut-2-yne (11). 1-(*p*-Methoxyphenoxy)-4-chlorobut-2-yne was secured in 61.9% yield, b.p. 148°/0.2mm, nmr (deuteriochloroform): 3.68 (s, 3H), 4.09 (t, 2H), 4.62 (t, 2H), 6.82 (m, 4H), and a molecular ion peak at m/e 210.

Anal. Calcd. for $C_{11}H_{11}ClO_2$: C, 62.71; H, 5.23. Found: C, 62.86; H, 5.32.

Synthesis of *N,N*-bis(4′-Aryloxy-2′-butynyl)anilines.

The appropriate aniline (0.1 mole), 1-aryloxy-4-chloro-2-butyne (0.02 mole) and potassium carbonate (0.1 mole, 13.8 g. in 100 ml. of water) was refluxed in 1-butanol (500 ml.) for 5 days with efficient stirring. Then the solvent was removed using a rotavapor. The residue was taken in chloroform (600 ml.). The chloroform solution was washed with plenty of water and dried (sodium sulfate). Removal of solvent gave a brown solid or viscous oil. The solid was recrystallized from acetone or chloroform-petroleum ether (30-60°). The viscous oil was triturated with acetone-ethanol mixture (80-100 ml.) and cooled to give a solid. If a solid was not obtained by this procedure then the viscous oil was purified by chromatography over neutral alumina (*e.g.*, compound 4 in Table I was obtained as a viscous oil). The *N,N*-bis (4′-aryloxy-2′-butynyl)-anilines thus obtained are listed in Table I.

When this reaction was performed by refluxing in ethanol or for shorter time (*e.g.*, 2-3 days) or without efficient stirring, a mixture of *N,N*-bis(4′-aryloxy-2′-butynyl)aniline, 1-aryloxy-4-anilino-2-butyne and unreacted aniline and 1-aryloxy-4-chloro-2-butyne was obtained. For example, when 2,4-dimethylaniline, 1-(*p*-methoxyphenoxy)-4-chloro-2-butyne and potassium carbonate were refluxed in 1-butyl alcohol for 3 days without efficient stirring, there was obtained a mixture of compound 4 of Table I and 1-(*p*-methoxyphenoxy)-4-(2′,4′-dimethylanilino)-2-butyne, m.p. 84°, nmr (deuteriochloroform): 2.08 (s, 3H), 2.23 (s, 3H), 3.25-3.60 (broad, 1H, disappeared on adding deutorium oxide), 3.70 (s, 3H), 3.94 (t, 2H), 4.60 (t, 2H), 6.32-7.20 (m, 7H), and a molecular ion peak at m/e 295.

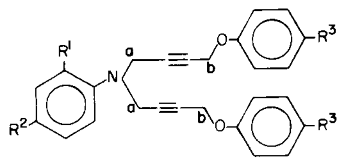
Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.28; H, 7.12; N, 4.74. Found: C, 77.21, H, 7.23; N, 4.50.

General Procedure for Oxidation and Rearrangement of *N,N*-bis-(4′-Aryloxy-2′-butynyl)anilines.

m-Chloroperbenzoic acid (12)(2.02 g., 0.01 mole) in methylene chloride (150 ml.) was slowly added to well-stirred solution of *N,N*-bis(4′-aryloxy-2′-butynyl)aniline derivative (0.01 mole) in methylene chloride (200 ml.). The solution was stirred at 22-23° for 12 hours more. Then the solution was washed with 5% aqueous potassium carbonate solution, salt water and dried (sodium sulfate). Removal of solvent gave a pale yellow solid which was recrystallized from methylene chloride-petroleum ether (30-60°). The indole derivatives thus obtained are listed in Table II.

(TABLE I)

N,N-bis(4′-Aryloxy-2′-butynyl)anilines

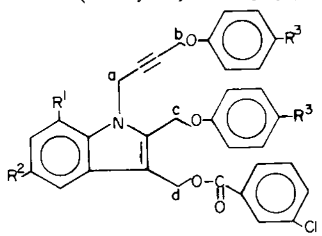


	R^1	R^2	R^3	M.P. (°C)	% Yield	Molecular Formula	Analysis Percent Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Nmr (deuteriochloroform): in δ a (t,4H)	b (t,4H)
1	H	Cl	Cl	100	62.8	$C_{26}H_{20}Cl_2NO_2$	64.40	4.13	2.89	64.68	4.14	2.88	4.05	4.62
2	H	OCH_3	Cl	79-80	60.8	$C_{27}H_{23}Cl_2NO_3$	67.50	4.79	2.92	67.69	4.81	2.92	4.00	4.65
3	H	CH_3	Cl	69.5-70.5	58.2	$C_{27}H_{23}Cl_2NO_2$	69.83	4.96	3.02	70.09	5.02	3.02	4.03	4.61
4(a)	CH_3	CH_3	OCH_3	(a)	50.0	$C_{30}H_{31}NO_4$	76.76	6.61	2.99	76.46	6.81	2.70	3.85	4.65
5	H	Br	OCH_3	115-116	53.8	$C_{28}H_{26}BrNO_4$	64.62	5.00	2.69	64.68	5.00	2.67	4.05	4.62
6	H	Cl	OCH_3	105	59.0	$C_{28}H_{26}ClNO_4$	70.66	5.47	2.94	70.83	5.68	2.73	4.02	4.57
7	H	CH_3	OCH_3	86	56.0	$C_{29}H_{29}NO_4$	76.48	6.37	3.08	76.65	6.38	3.10	4.04	4.58
8	H	OCH_3	OCH_3	99	57.3	$C_{29}H_{29}NO_5$	73.89	6.16	2.97	73.62	6.34	2.70	3.95	4.58

(a) Compound 4 would not solidify, purified by chromatography over neutral alumina.

(TABLE II)

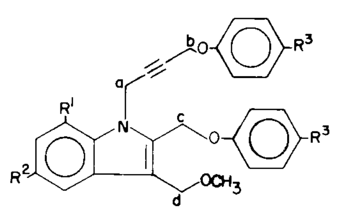
1-(4′-Aryloxy-2′-butynyl)-2-(aryloxymethyl)-3-(*m*-chlorobenzoylmethyl)indoles



	R^1	R^2	R^3	M.P. (°C)	% Yield	Molecular Formula	Analysis Percent Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Nmr (deuteriochloroform): in δ a (t, 2H)	b (t, 2H)	c (s, 2H)	d (s, 2H)
1	H	Cl	Cl	152.5	86.0	$C_{33}H_{23}Cl_4NO_4$	61.97	3.60	2.19	61.88	3.62	2.12	5.02	4.60	5.35	5.61
2	H	OCH_3	Cl	145	85.1	$C_{34}H_{26}Cl_3NO_5$	64.30	4.09	2.20	64.13	4.09	2.08	4.99	4.59	5.30	5.62
3	H	CH_3	Cl	139	87.3	$C_{34}H_{26}Cl_3NO_4$	65.96	4.20	2.26	65.92	4.26	2.13	5.01	4.60	5.34	5.63
4	CH_3	CH_3	OCH_3	142-44	72.0	$C_{37}H_{34}ClNO_6$	71.21	5.45	2.35	71.31	5.45	2.18	5.20	4.56	5.24	5.55
5	H	Br	OCH_3	92-93	83.0	$C_{35}H_{29}BrClNO_6$	62.27	4.30	2.08	62.02	4.30	1.99	5.02	4.56	5.30	5.55
6	H	Cl	OCH_3	96-98	87.3	$C_{35}H_{29}Cl_2NO_6$	66.66	4.68	2.26	66.74	4.62	2.28	4.98	4.54	5.26	5.52
7	H	CH_3	OCH_3	117	88.6	$C_{36}H_{32}ClNO_6$	70.88	5.25	2.30	71.14	5.16	2.36	4.95	4.51	5.25	5.55
8	H	OCH_3	OCH_3	127	88.0	$C_{36}H_{32}ClNO_7$	69.06	5.11	2.24	69.29	5.06	2.30	4.96	4.53	5.25	5.57

(TABLE III)

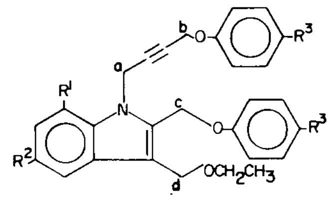
1-(4'-Aryloxy-2'-butynyl)-2-(aryloxymethyl)-3-(methoxymethyl)indole



	R^1	R^2	R^3	M.P. (°C)	% Yield	Molecular Formula	Analysis Percent Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Nmr (deuteriochloroform): in δ a (t, 2H)	b (t, 2H)	c (s, 2H)	d (s, 2H)
1	H	Cl	Cl	157	81.7	$C_{27}H_{22}Cl_3NO_3$	62.97	4.27	2.72	62.88	4.35	2.65	5.00	4.60	5.22	4.66
2	H	OCH_3	Cl	114	80.0	$C_{28}H_{25}Cl_2NO_4$	65.88	4.90	2.74	65.91	4.96	2.68	4.96	4.57	5.20	4.58
3	H	CH_3	Cl	113	80.4	$C_{28}H_{25}Cl_2NO_3$	68.01	5.06	2.83	68.16	5.06	2.74	4.97	4.56	5.20	4.60
4	CH_3	CH_3	OCH_3	130	70.0	$C_{31}H_{33}NO_5$	74.55	6.61	2.81	74.27	6.62	2.68	5.19	4.55	5.14	4.62
5	H	Br	OCH_3	116	85.4	$C_{29}H_{28}BrNO_5$	63.27	5.09	2.54	63.57	5.11	2.61	5.01	4.56	5.20	4.63
6	H	Cl	OCH_3	107-108	80.0	$C_{29}H_{28}ClNO_5$	68.84	5.54	2.77	69.05	5.41	2.85	4.97	4.54	5.15	4.60
7	H	CH_3	OCH_3	120	82.4	$C_{30}H_{31}NO_5$	74.23	6.39	2.89	74.08	6.17	2.93	4.96	4.52	5.17	4.64
8	H	OCH_3	OCH_3	126	79.8	$C_{30}H_{31}NO_6$	71.86	6.19	2.79	71.88	6.14	2.93	4.96	4.53	5.17	4.65

(TABLE IV)

1-(4'-Aryloxy-2'-butynyl)-2-(aryloxymethyl)-3-(ethoxymethyl)indole



	R^1	R^2	R^3	M.P. (°C)	% Yield	Molecular Formula	Analysis Percent Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Nmr (deuteriochloroform): in δ a (t, 2H)	b (t, 2H)	c (s, 2H)	d (s, 2H)
1	H	Cl	Cl	91	85.2	$C_{28}H_{24}Cl_3NO_3$	63.58	4.54	2.65	63.31	4.47	2.68	4.95	4.57	5.18	4.68
2	H	OCH_3	Cl	116	82.0	$C_{29}H_{27}Cl_2NO_4$	66.41	5.15	2.67	66.56	5.15	2.63	4.90	4.52	5.15	4.68
3	H	CH_3	Cl	102-3	82.6	$C_{29}H_{27}Cl_2NO_3$	68.50	5.31	2.76	68.35	5.37	2.77	4.92	4.53	5.17	4.60
4	CH_3	CH_3	OCH_3	109	72.0	$C_{32}H_{35}NO_5$	74.85	6.82	2.73	75.15	6.79	2.84	5.15	4.54	5.13	4.67
5	H	Br	OCH_3	113	83.3	$C_{30}H_{30}BrNO_5$	63.83	5.32	2.48	63.74	5.15	2.44	5.00	4.56	5.20	4.66
6	H	Cl	OCH_3	109	84.6	$C_{30}H_{30}ClNO_5$	69.30	5.77	2.69	69.50	4.81	2.70	4.96	4.54	5.16	4.65
7	H	CH_3	OCH_3	105-106	84.0	$C_{31}H_{33}NO_5$	74.55	6.61	2.81	74.78	6.57	2.87	4.97	4.54	5.18	4.60

General Procedure for Alcoholysis of 1-(4'-Aryloxy-2-butynyl)-2-(aryloxymethyl)-3-(*m*-chlorobenzoylmethyl)indole.

The alcoholysis was performed by refluxing the metachlorobenzoylmethyl derivative (0.001 mole) in absolute alcohol (methanol or ethanol 150 ml.) for 1-2 hours. The solvent was removed *in vacuo*. The residual solid was dissolved in chloroform (50 ml.), washed with 10% potassium carbonate solution, water and dried (sodium sulfate). Removal of solvent gave a white solid which was recrystallized from the same alcohol used in the reaction. The derivatives thus obtained are listed in Table III and IV.

Reaction of *N,N*-bis[4'-(*p*-Chlorophenoxy)-2'-butynyl]-4-methoxyaniline with Methyl Iodide.

N,N-bis[4'-(*p*-Chlorophenoxy)-2'-butynyl]-4-methoxyaniline (0.005 mole, 2.40 g.) in dry chloroform (200 ml.) was refluxed with methyl iodide (0.01 mole, 1.42 g.) for 2 days using a calcium chloride guard tube. Two tenths g. of white solid was obtained, m.p. 264°, nmr (deuteriochloroform): 3.62 (s, 9H), 3.84 (s, 3H), 7.02-7.20 (d, 2H), 7.82-8.03 (d, 2H).

Anal. Calcd. for $C_{10}H_{16}NIO$: C, 40,96; H, 5.46; N, 4.78. Found: C, 40.75; H, 5.26; N, 4.69.

When more methyl iodide (5 g.) was added to the filtrate and refluxed for 5 days more, more of *p*-methoxyphenyltrimethylammonium iodide (1.20 g.) formed. Solvent was removed from the filtrate to give a brown oil, 1-(*p*-chlorophenoxy)-4-iodo-2-butyne. This oil was refluxed with sodium *p*-chlorophenoxide in 90% ethanol to give 1,4-bis(*p*-chlorophenoxy)-2-butyne (13).

Acknowledgments.

We wish to thank the Research Corporation for partial support of this work.

REFERENCES

(1) References 2 and 3 form Parts I and II of this series of investigations.

(2) B. S. Thyagarajan, J. B. Hillard, K. V. Reddy and K. C. Majumdar, *Tetrahedron Letters*, 1999 (1974).

(3) J. Hillard, K. V. Reddy, K. C. Majumdar and B. S. Thyagarajan, *J. Heterocyclic Chem.*, **11**, 0000 (1974).

(4) W. J. Welstead Jr., H. F. Stauffer Jr., and L. F. Sancilio, *J. Med. Chem.*, **17**, 544 (1974).

(5) D. R. Olson, W. J. Wheeler and J. N. Wells, *J. Med. Chem.*, **17**, 167 (1974).

(6) The early observations on this cleavage were made by Mr. S. E. Thomas, NDEA Fellow at University of Idaho, 1970-1971.

(7) A. Padwa and L. Hamilton, *J. Org. Chem.*, **31**, 1995 (1966).

(8) J. K. Stille and D. D. Whitehurst, *J. Am. Chem. Soc.*, **86**, 4871 (1964).

(9) J. Ciabattoni, R. A. Campbell and C. A. Reiner, *ibid.*, **92**, 3826 (1970).

(10) K. C. Majumdar and B. S. Thyagarajan, *J. Heterocyclic Chem.*, **9**, 489 (1972).

(11) K. C. Majumdar and B. S. Thyagarajan, *Int. J. Sulfur Chem.*, **2**, 93 (1972).

(12) *m*-Chloroperbenzoic acid (85%) was used as obtained from the Aldrich Chemical Co. Inc.

(13) B. S. Thyagarajan, K. K. Balasubramanian and R. Bhima Rao, *Tetrahedron*, **21**, 2289 (1965).