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SYNTHESES OF SOME SUBSTITUTED DI-INDOLYLMETHANES IN AQUEOUS MEDIUM AT ROOM TEMPERATURE

A. KAMAL and A. ALI QURESHI
West Regional Laboratories, Pakistan S.I.R., Lahore

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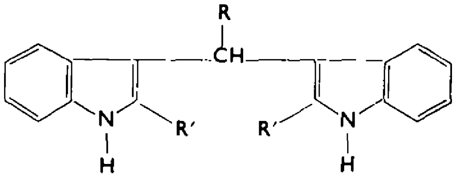
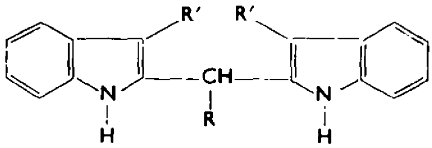
Abstract—Syntheses of di-indolylmethane and di-indolylmethane with various aliphatic, aromatic, substituted aromatic and heterocyclic groups (viz: methyl; propenyl; phenyl; α-naphthyl; 2-nitrophenyl; styryl; 4-nitrophenyl; 3:4-dimethoxyphenyl; 2-hydroxyphenyl: 3-hydroxyphenyl; 4-methoxyphenyl and α-furyl), as substituents at the methylene carbon. has been carried out in aqueous medium, at various pH.

IN CONTINUATION of the series,[1] the condensation of various aldehydes with indole, 2-methylindole and 3-methylindole in aqueous media at various pH has been investigated. In all cases *di*-indolylmethanes of the type (A) and (B) were obtained.



I. R = H— R′ = H.
II. R = CH_3— R′ = H.
III. R = $CH_3CH{=}CH$— R′ = H.
IV. R = C_6H_5— R′ = H.
V. R = α-naphthyl: ($C_{10}H_7$)— R′ = H.
VI. R = m-$NO_2.C_6H_4$— R′ = H.
VII. R = $C_6H_5CH{=}CH$— R′ = H.
VIII. R = p-$NO_2.C_6H_4$— R′ = H.
IX. R = 3:4-$(CH_3O)_2.C_6H_3$— R′ = H.
X. R = m-$OH.C_6H_4$— R′ = H.
XI. R = o-$OH.C_6H_4$— R′ = H.
XII. R = p-$CH_3O.C_6H_4$— R′ = H.
XIII. R = α-Furyl— R′ = H.
XIV. R = C_6H_5— R′ = CH_3.

(A)



XV. R = C_6H_5— R′ = CH_3.

(B)

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[1] A. Kamal, A. Ali Qureshi and I. Ahmad, *Tetrahedron*, **19** (1963). May issue.

TABLE 1

Aldehyde employed (0·01 mole)	Product obtained (Mol. formula)	Crystallizing medium, shape of crystals and colour of product	Solubility**		M.P.	Yield in gm and % (based on aldehyde)			
			Soluble	Insoluble		(H_2SO_4) pH 1·0	(Malonic acid) pH 1·5	(Acetic acid) pH 2·5	(Urea) pH 7·2
Fomaldehyde. (40%; 0·75 g);	Di-indolyl-3-methane (I); ($C_{17}H_{14}N_2$).	Dil. ethanol; needles.	*a*, *b*, *d*, *f*, *g*, *j*.	*c*, *i*.	164° (Clear melt)	— 40	1·41 57	1·69 68	1·53 62
Acetaldehyde. (0·44 g)	Methyl-di-indolyl-3-methane (II); ($C_{18}H_{16}N_2$).	Benzene-light-petroleum*; needles.	*a*, *b*, *d*, *f*, *g*, *j*.	*c*, *e*, *i*.	156° (Clear melt)	— 27	1·46 56	1·51 58	1·05 40
Crotonaldehyde. (0·7 g)	Di-indolyl-3-propenyl methane (III); ($C_{20}H_{18}N_2$).	Ethyl acetate–light-petroleum*; needles.	*a*, *b*, *d*, *f*, *g*, *j*.	*c*, *e*, *i*.	130° (Clear melt)	— 22	0·91 35	1·98 69	1·21 42
Benzaldehyde. (1·06 g)	Phenyl-di-indolyl-3-methane (IV); ($C_{23}H_{18}N_2$).	Ethyl acetate–light-petroleum*; needles.	*a*, *b*, *f*, *g*, *j*.	*c*, *d*, *e*, *h*, *i*.	125° (Clear melt). Lit[8]. (120–21°)	— 39	1·52 47	2·30 71	1·93 60

α-Naphthaldehyde. (1·56 g)	α-Naphthyl-di-indolyl-3-methane (V); ($C_{27}H_{20}N_2$).	Benzene; microscopic plates.	*a*, *b*, *f*, *g*, *j*.	*c*, *e*, *h*, *i*.	252° (Dec)	—	1·9 51	2·01 54	1·4 38
m-Nitrobenzaldehyde. (1·51 g)	(3′-Nitrophenyl)-di-indolyl-3-methane (VI); ($C_{23}H_{17}O_2N_3$).	Ether–ethanol plates.	*a*, *f*, *g*, *j*.	*c*, *e*, *h*, *i*.	264° (Dec). Lit.[4] 260° (Dec)	—	1·85 50·3	2·23 60·7	1·57 43
Cinnamaldehyde. (1·32 g)	styryl-di-indolyl-3-methane. (VII); ($C_{25}H_{20}N_2$).	Ether–light-petroleum*; needles.	*a*, *b*, *c*, *e*, *f*, *g*, *j*.	*c*, *h*, *i*.	99° (Clear melt)	—	2·11 60·8	2·23 64	1·82 52
p-Nitrobenzaldehyde. (1·51 g)	(4′-Nitrophenyl)-di-indolyl-3-methane (VIII); ($C_{23}H_{17}O_2N_3$).	Ethyl acetate–light-petroleum*; yellow needles.	*a*, *b*, *c*, *f*, *g*, *j*.	*e*, *h*, *i*.	225° (Dec)	—	1·27 34	2·54 69	1·47 40
Veretraldehyde. (1·66 g)	(3′,4′-Dimethoxy-phenyl)-di-indolyl-3-methane (IX); ($C_{25}H_{22}O_2N_2$).	Ethyl acetate–light-petroleum*; needles.	*a*, *b*, *d*, *e*, *f*, *g*, *j*.	*h*, *i*.	195° (Dec)	—	1·97 52	2·52 65	1·47 39

TABLE 1 (contd.)

Aldehyde employed (0·01 mole)	Product obtained (Mol. formula)	Crystallizing medium, shape of crystals and colour of product	Solubility†		M.P.	Yield in gm and % (based on aldehyde).			
			Soluble	Insoluble		(H_2SO_4) pH 1·0	(Malonic acid) pH 1·5	(Acetic acid) pH 2·5	(Urea) pH 7·2
Salicylaldehyde. (1·22 g)	(2′-Hydroxyphenyl)-di-indolyl-3-methane. (X); ($C_{23}H_{18}O_1N_2$).	Benzene–light-petroleum; needles.	*a*, *b*, *d*, *e*, *f*, *g*, *j*.	*h*, *i*.	349° (Dec)	–	2·11 62	2·25 66	1·34 39
m-Hydroxybenzaldehyde. (1·22 g)	(3′-Hydroxyphenyl)-di-indolyl-3-methane. (XI); ($C_{23}H_{18}O_1N_2$).	Benzene–light-petroleum*; needles.	*a*, *b*, *d*, *e*, *f*, *g*, *j*.	*c*, *h*, *i*.	98° (Clear melt).	– –	0·71 21	2·07 61	0·37 11
Anisaldehyde. (1·36 g)	(4′-Methoxyphenyl)-di-indolyl-3-methane. (XII); ($C_{24}H_{20}O_1N_2$).	Ethyl acetate–light-petroleum*; needles.	*a*, *b*, *d*, *f*, *g*, *j*.	*c*, *e*, *h*, *i*.	189° (Clear melt).	– –	1·12 31	2·19 62	1·53 43
Furfural. (0·93 g)	α-Furyl-di-indolyl-3-methane (XIII); ($C_{21}H_{16}O_1N_2$).	Benzene–ligroin; needles.	*a*, *b*, *c*, *d*, *e*, *f*. *g*, *j*.	*h*, *i*.	325° (Dec)	– –	1·47 47	2·12 68	1·23 39

* = b.p. 60–80°

† = *a*—acetone,
b—benzene,
c—carbontetrachloride,
d—chloroform,
e—ether,
f—ethylacetate,
g—ethylalcohol,
h—ligroin,
i—light petroleum (60–80°C.)
j—methylalcohol.

TABLE 2

Product	Molecular formula (Mol. wt.)	Required	Analysis		(Found)	UV absorption bands in 95% ethanol	
		C%	H%	O%	N%	Mol. wt. (Rast)	λ_{max} (log ε) in mμ	λ_{min} (log ε) in mμ
Di-indolyl-3-methane (I).	$C_{17}H_{14}N_2$ (246)	82·90* (82·27)	5·73 (5·73)	—	11·37 (11·59)	236	280 (4·08)	245 (3·62)
Methyl-di-indolyl-3-methane (II).	$C_{18}H_{16}N_2$ (260)	83·04 (82·92)	6·20 (6·5)	—	10·76 (10·57)	270	280 (4·40)	250 (4·21)
Di-indolyl-3, propenyl-methane (III).	$C_{20}H_{18}N_2$ (286)	83·88 (83·91)	6·34 (6·42)	—	9·78 (9·75)	285	245 (4·30)	240 (4·27) 290 (4·08)
Phenyl-di-indolyl-3-methane (IV)	$C_{23}H_{18}N_2$ (322)	85·68* (85·7)	5·63 (5·47)	—	8·69 (8·90)	310	280 (3·85)	255 (3·68)
α-Naphthyl-di-indolyl-3-methane (V)	$C_{27}H_{20}N_2$ (372)	87·06 (87·0)	5·41 (5·32)	—	7·52 (7·61)	370	280 (4·49)	250 (410)
3′-Nitrophenyl-di-indolyl-3-methane (VI).	$C_{23}H_{17}O_2N_3$ (367)	75·19* (75·25)	4·66 (4·6)	8·71 (8·75)	11·44 (11·45)	359	270 (4·35)	240 (4·22)
Styryl-di-indolyl-3-methane (VII).	$C_{25}H_{20}N_2$ (348)	86·17 (86·25)	5·97 (5·65)	—	8·04 (8·1)	340	226 (4·83) with shoulder at 246† (3·84)	
(4′-Nitrophenyl)-di-indolyl-3-methane (VIII)	$C_{23}H_{17}O_2N_3$ (367)	75·19 (75·35)	4·66 (4·47)	8·71 (8·75)	11·44 (11·52)	354	275 (4·78)	240 (4·54)

TABLE 2 (contd)

Product	Molecular formula (Mol. wt.)	Required		Analysis		(Found)	UV absorption bands in 95% ethanol	
		C%	H%	O%	N%	Mol wt. (Rast)	λ_{max} (log ε) in mμ	λ_{min} (log ε) in mμ
(3′:4′-Dimethoxyphenyl)-di-indolyl-3-methane (IX).	$C_{25}H_{22}O_2N_2$ (382)	78·51 (78·76)	5·8 (5·3)	8·37 (8·45)	7·33 (7·4)	370	280 (4·77) 235 (4·99)	310 (3·16) 255 (4·35)
(2′-Hydroxyphenyl)-di-indolyl-3-methane (X).	$C_{23}H_{18}O_1N_2$ (338)	81·63 (81·76)	5·36 (5·4)	4·73 (4·47)	8·28 (8·42)	327	280 (4·22)	245 (3·87)
(3′-Hydroxyphenyl)-di-indolyl-3-methane (XI).	$C_{23}H_{18}O_1N_2$ (338)	81·63 (81·47)	5·36 (5·3)	4·73 (4·78)	8·28 (8·29)	335	255 (4·40)	275 (3·54) 235 (4·12)
(4′-Methoxyphenyl)-di-indolyl-3-methane (XII).	$C_{24}H_{20}O_1N_2$ (352)	81·79 (81·52)	5·72 (5·89)	4·54 (4·50)	7·95 (8·01)	345	280 (4·19)	255 (3·96)
α-Furyl-di-indolyl-3-methane (XIII).	$C_{21}H_{16}O_1N_2$ (312)	80·75 (81·01)	5·16 (5·23)	5·12 (5·12)	8·97 (8·92)	302	280 (4·23)	250 (4·17)

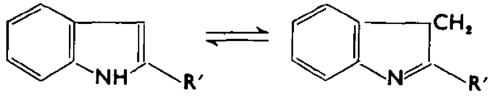
* Calculated for. † Determined with Beckman Spectrophotometer Model D.B.

The literature reveals the syntheses of only a few substituted di-indolyl-methanes. For instance phenyl-di-indolyl-3-methane,[2] phenyl-di-(2-methyl-indolyl)-3-methane[3] and (3′-nitro-phenyl)-di-indolyl-3-methane[4] have been prepared by interaction of the corresponding MgI or MgBr Grignard complexes of indole and 2-methylindole with the appropriate aldehydes. In another method to obtain phenyl-di-(3-methyl-indolyl)-2-methane, skatol was heated with benzaldehyde in presence of anhydrous zinc chloride[5]—a repetition of the method of Freund and Lebach[6] employed earlier. In another method Burr and Gortner[7] obtained phenyl-di-(2-methyl-indolyl)-3-methane by heating the sulphate of phenyl-α-methylindolidenemethane in water.

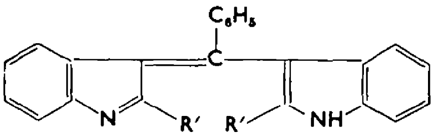
Two molecules of indole react with one molecule each of various aliphatic, aromatic and substituted aromatic aldehydes and also a heterocyclic aldehyde (furfural) in water at various pH, yielding the corresponding substituted di-indolyl-methanes. It has been noted that the best yields are obtained at pH 2·5 employing acetic acid. Any change in pH by using malonic acid (pH 1·5), or urea (pH 7·2),* and sulphuric acid (pH 1) which was employed for the condensation of indole with formaldehyde, acetaldehyde, crotonaldehyde and benzaldehyde only, resulted in decreased yields. All these condensations were effected over ten day periods and any increase in the time did not improve the yields. No condensation takes place in water alone.

Condensation of benzaldehyde with 2 moles each of 2-methyl- and 3-methyl-indole yields the phenyl-di-(2-methyl-indolyl)-3-methane (XIV; m.p. 245°) and phenyl-di-(3-methyl-indolyl)-2-methane, (XV; m.p. 160°). Utilization of 1 mole each of indole and an aldehyde yields a molecule of the corresponding methylene substituted di-indolyl-methane together with unreacted aldehyde. No intermediate was isolated in any of the condensations.

It is evident that in the condensations, indole reacts in the tautomeric form C(R′ = H) and not D(R′ = H). As further confirmation phenyl di-(2-methyl-indolyl)-3-methane (XIV) was oxidized with ferric chloride in glacial acetic acid[8], the product



C D



XVI

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* We employed 0·01 mole each of acetic acid, malonic acid and urea in 50 ml of water.

[2] R. Majima and M. Kotake, *Ber. Dtsch. Chem. Ges.* **55**, 3869 (1924).

[3] Q. Mingoia, *Gaz. Chim. Ital.*, **56**, 775 (1926).

[4] Q. Mingoia, *Gaz. Chim. Ital.*, **56**, 780 (1926).

[5] M. Hadano, *Chem. Zbl.*, **11**, 2557 (1928). *J. Pharm. Soc. Japan.* **48**, 9S, 115; M. Passerini and T. Bonciani, *Gaz. Chim. Ital.*, **63**, 142 (1933).

[6] M. Freund and G. Lebach, *Ber. Dtsch. Chem. Ges.*, **38**, 2646 (1905).

[7] T. O. Burr and R. A. Gortner, *J. Amer. Chem. Soc.*, **46**, 1227 (1924).

[8] E. Fischer, *Ann. Chem. Liebigs.*, **242**, 374. E. Fischer and P. Wagner, *Ber. Dtsch. Chem. Ges.*, **20**, 817 (1887).

(m.p. 270°) being identical to an authentic sample of phenyl-di-(2-methylindolidene)-3-methane, m.p. 270° (XVI; $R' = CH_{3}$—) prepared in accordance with the method of Fischer & Wagner.[9]

As all the condensation products described manifest similar chemical behaviour and uniform U.V. absorption patterns, they may be regarded as having constitutions analogous to A or B depending on the indole employed.

EXPERIMENTAL

All yields are based on the aldehydes employed. All m.ps. are corrected. U.V. absorption spectra were determined with a Beckman Spectrophotometer Model D.U. in 95% ethanol.

General method

Condensation of indole with aldehydes. To powdered indole (2·34 g; 0·02 mole) suspended in water (50 ml) containing acetic acid (0·6 g; 0·01 mole; pH 2·5) or malonic acid (1·04 g; 0·01 mole; pH 1·5) or urea (0·6 g; 0·01 mole; pH 7·2) aldehyde (0·01 mole) was added with occasional shaking and left to stand (10 days). If an oil separated it was extracted with ethyl acetate; if a solid separated it was collected (suction) and crystallized.

The quantity (in gm and molar ratio) of each of the aldehydes, the name of the solvent from which each product was crystallized, solubilities of the product, the shape of the crystals, m.ps. and yields are shown in Table 1. The elemental analyses of the products as well as their U.V. Spectral analyses are shown in Table 2. All these compounds are light sensitive and gradually colour (yellow to deep orange and red and in the case of α-furyldi-indolyl-3-methane (XIII) to deep blackish brown) on storage.

Phenyl-di-(2-methylindolyl)-3-methane: (XIV). To powdered 2-methylindole (2·62 g; 0·02 mole) suspended in water (50 ml) containing acetic acid (0·6 g; 0·01 mole; pH 2·5) or malonic acid (1·04 g; 0·01 mole; pH 1·5) or urea (0·6 g; 0·01 mole; pH 7·2), benzaldehyde (1·06 g; 0·01 mole) was added, and occasionally shaken and left to stand (10 days). The product separated as a viscous oil and was isolated with ethyl acetate, yield at pH 2·5 (acetic acid), 2·1 g; (60%) and crystallized from ethyl acetate–ligroin in microscopic needles; 1·78 g; (50·9%); m.p. 245° (dec). Yield at pH 1·5 (malonic acid) 0·59 g; (17%) and at pH 7·2 (Urea), 0·94; (27%). Lit.[7] m.p. 247° (dec); mixed m.p. undepressed. It is easily soluble in acetone, benzene, ethyl acetate, ethanol and methanol; and insoluble in light-petroleum (60–80°) and ligroin. Found: C, 85·57; H, 6·40; N, 7·90%; M.W. (Rast), 340. Calc. for Phenyl-di-(2-methylindolyl)-3-methane: $C_{25}H_{22}N_{2}$, (M.W. 350): C, 85·68; H, 6·33; N, 7·99%).

Its U.V. absorption bands are at λ_{max} 280 mμ (log ε 4·42) and λ_{min} 225 mμ (log ε 4·25).

Phenyl-di-(3-methylindolyl)-2-methane: (XV). This was prepared from 3-methylindole as for XIV above. The separated crystalline material m.p. 157° (clear melt), yield at pH 2·5 (acetic acid), 2·7 g; (77%) recrystallized from benzene-light-petroleum (60–80°) in needles m.p. 160° (clear melt) undepressed on admixture with an authentic sample.[5] Yield at pH 1·5 (malonic acid) was 1·23 g; (35%) and at pH 7·2 (urea), 0·63 g; (18%). It is easily soluble in chloroform, ethyl acetate, ethanol and methanol, benzene and insoluble in carbon tetrachloride and light-petroleum (60–80°). The U.V. absorption bands are at λ_{max} 285 mμ (log ε 4·68); 235 mμ (log ε 4·13) and λ_{min} 310 mμ (log ε 3·32) and 260 mμ (log ε 4·30).

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All analysis were carried out by Dr. A. Bernhardt, Microanalytisches Laboratorium, 22a, Mulheim, (Ruhr), West Germany. Substances were dried over phosphorus pentoxide at 50°, in high vacuum before analysis.

[9] E. Fischer and P. Wagner, *Ber. Dtsch. Chem. Ges.*, **20**, 815 (1887).