1027. *Carcinogenic Nitrogen Compounds. Part XXXVIII.*[1] *The Condensation of Nuclear Aromatic and Heterocyclic Aldehydes with* meso-*Methylated Benz*[a]- *and* -[c]*acridines.*

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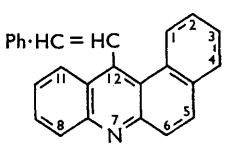
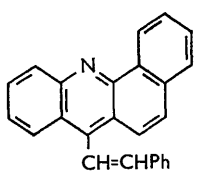
Benz[*a*]acridines methylated in position 12 and benz[*c*]acridines methylated in position 7 condense with aromatic, thiophen, and pyridine aldehydes, to give the corresponding *trans*-styryl compounds, which were required for examination of potential carcinogenicity.

Numerous 7-methylbenz[*c*]acridines are known to be potent carcinogens, and in the related, biologically weaker, benz[*a*]acridine series the few active compounds are also those substituted in *meso*-positions.[2] Further, it is known that in similarly built carcinogenic hydrocarbons (*e.g.*, 1,2-benzopyrene) biological activity is maintained when the *meso*-methyl group is replaced by styryl.[3] It was therefore of interest to prepare *meso*-styryl derivatives of angular benzacridines; and, for this, the reactivity of *meso*-methylated benzacridines towards various nuclear aromatic aldehydes was examined.

12-Methylbenz[*a*]acridine and 7-methylbenz[*c*]acridine reacted readily with benzaldehyde in the presence of acetic anhydride to give the corresponding styryl compounds (I) and (II). These had the *trans*-configuration, as was shown by nuclear magnetic re-



(I)



(II)

sonance spectroscopy. The spectrum of compound (I) showed at δ (p.p.m.) 6·85 a doublet corresponding to a coupling constant $J = 17$ c./sec., characteristic of *trans*-ethylenic protons;[4] similarly, the spectrum of compound (II) showed a doublet (δ 6·91) corresponding to a coupling constant of $J = 16{\cdot}5$ c./sec. The *trans*-configuration was confirmed by the infrared spectra; compound (I) had a band at 980 cm.$^{-1}$, and (II) had a band at 975 cm.$^{-1}$, typical of *trans*-compounds. The ultraviolet absorption spectra of compounds (I) and (II) closely resembled each other; the bathochromic effect produced by conjugation of the benzacridine nucleus with a styryl group was relatively small.

Oxidation with potassium permanganate in acetone readily converted the products

[1] Part XXXVII, Buu-Hoï, Jacquignon, and Hoeffinger, *J.*, 1963, 4754.
[2] Lacassagne, Buu-Hoï, Daudel, and Zajdela, *Adv. Cancer Res.*, 1956, **4**, 315.
[3] Lacassagne, Buu-Hoï, and Zajdela, *Compt. rend.*, 1957, **245**, 876.
[4] Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p. 85.

(I) and (II) into the corresponding benz[*c*]acridinecarboxylic acids, this route being more convenient than those reported earlier.[5]

The condensation was extended to methyl homologues of these methylbenzacridines and to other aldehydes (see Table). The condensation products from the pyridinealdehydes gave dipicrates.

Attempts to condense aromatic aldehydes with the *meso*-methylated bisangular 14-methyldibenz[*a*, *j*]acridine failed, most of the starting material being recovered.

Tests for carcinogenicity will be reported elsewhere.

trans-Styrylbenzacridines and analogues.

Substance	M. p.	Colour of base in H_2SO_4 or of picrate	Found (%) C	H	N	Formula	Required (%) C	H	N
Benz[a]*acridines*									
12-Styryl	163°	Orange	90·5	5·2	4·2	$C_{25}H_{17}N$	90·6	5·1	4·2
picrate *	268 (dec. >245)	Golden-yellow	—	—	10·2	$C_{31}H_{20}N_4O_7$	—	—	10·0
10-Methyl-12-styryl	152	Orange	90·2	5·8	4·0	$C_{26}H_{19}N$	90·4	5·5	4·1
picrate *	297 (dec. >270)	Orange-yellow	—	—	9·9	$C_{32}H_{22}N_4O_7$	—	—	9·8
9-Methyl-12-styryl	186	Orange	90·3	5·4	4·1	$C_{26}H_{19}N$	90·4	5·5	4·1
picrate *	264 (dec. >240)	Golden-yellow	—	—	9·7	$C_{32}H_{22}N_4O_7$	—	—	9·8
8-Methyl-12-styryl	157	Orange	90·2	5·5	4·2	$C_{26}H_{19}N$	90·4	5·5	4·1
picrate †	251 (dec. >225)	Ochre	—	—	10·2	$C_{32}H_{22}N_4O_7$	—	—	9·8
12-2′-Methoxystyryl	203	Red	86·0	5·3	3·8	$C_{26}H_{19}NO$	86·4	5·3	3·8
picrate *	246 (dec. >235)	Ochre	—	—	9·6	$C_{32}H_{22}N_4O_8$	—	—	9·5
12-[2-(1-Naphthyl)ethylidene]	278	Orange-red	91·1	5·0	4·0	$C_{29}H_{19}N$	91·3	5·0	3·7
picrate *	252 (dec. >245)	Saffron	—	—	9·2	$C_{35}H_{22}N_4O_7$	—	—	9·2
12-[2-(2-Thienyl)ethylidene]	197	Blood-red	81·9	4·4	3·9	$C_{23}H_{15}NS$	81·9	4·5	4·1
picrate *	233 (dec. >200)	Red	—	—	9·8	$C_{29}H_{18}N_4O_7S$	—	—	9·9
12-[2-(3-Pyridyl)ethylidene]	179	Yellow	86·3	5·1	8·4	$C_{24}H_{16}N_2$	86·7	4·8	8·4
picrate *	228 § (dec.)	Orange	—	—	14·3	$C_{36}H_{22}N_8O_{14}$	—	—	14·2
Benz[c]*acridines*									
7-Styryl	189	Orange	90·5	5·2	4·4	$C_{25}H_{17}N$	90·6	5·1	4·2
picrate †	221 (dec. >190)	Orange	—	—	10·0	$C_{31}H_{20}N_4O_7$	—	—	10·0
9-Methyl-7-styryl	201	Red	90·7	5·4	4·1	$C_{26}H_{19}N$	90·4	5·5	4·1
picrate *	243 (dec. >235)	Golden-yellow	—	—	9·9	$C_{32}H_{22}N_4O_7$	—	—	9·8
10-Methyl-7-styryl	163	Orange-red	90·5	5·5	4·2	$C_{26}H_{19}N$	90·4	5·5	4·1
picrate ‡	276 (dec. >245)	Orange-yellow	—	—	9·5	$C_{32}H_{22}N_4O_7$	—	—	9·8
7-2′-Methoxystyryl	184	Vermilion	86·7	5·6	3·7	$C_{26}H_{19}NO$	86·4	5·3	3·9
picrate *	243 (dec. >235)	Brick-red	—	—	9·7	$C_{32}H_{22}N_4O_8$	—	—	9·5
7-[2-(1-Naphthyl)ethylidene]	213	Orange-red	91·2	5·1	3·7	$C_{29}H_{19}N$	91·3	5·0	3·7
picrate *	263 (dec. >225)	Orange-red	—	—	9·8	$C_{35}H_{22}N_4O_7$	—	—	9·2
7-[2-(2-Thienyl)ethylidene]	194	Blood-red	81·6	4·6	4·1	$C_{23}H_{15}NS$	81·9	4·5	4·1
picrate ‡	236 (dec.)	Red	—	—	9·6	$C_{29}H_{18}N_4O_7S$	—	—	9·9
10-Methyl-7-[2-(2-thienyl)ethylidene]	168	Dark red	82·4	4·8	4·0	$C_{24}H_{17}NS$	82·1	4·8	4·0
picrate *	257 (dec. >235)	Red	—	—	9·8	$C_{30}H_{20}N_4O_7S$	—	—	9·7
7-[2-(3-Pyridyl)ethylidene]	164	Orange-yellow	86·7	4·9	8·5	$C_{24}H_{16}N_2$	86·7	4·8	8·4
dipicrate *	247 (dec.)	Orange	—	—	14·0	$C_{36}H_{22}N_8O_{14}$	—	—	14·2
7-[2-(4-Pyridyl)ethylidene]	178	Orange-yellow	86·7	4·8	8·3	$C_{24}H_{16}N_2$	86·7	4·8	8·4
dipicrate *	261 (dec. >255)	Orange	—	—	14·0	$C_{36}H_{22}N_8O_{14}$	—	—	14·2

* Recryst. from nitrobenzene. † Recryst. from *o*-dichlorobenzene. ‡ Recryst. from chlorobenzene. § Melted first at *ca.* 180° and resolidified before melting again.

Experimental

Condensation of Aldehydes with meso-*Methylbenzacridines.*—The acridines were prepared from the corresponding secondary diarylamines by the Bernthsen reaction as modified by

[5] Saftien, *Ber.*, 1925, **58**, 1958; Stollé, Bergdoll, Luther, and Wacker, *J. prakt. Chem.*, 1930, **128**, 1.

Buu-Hoï *et al.*[6] A mixture of the acridine (0·03 mole), the aromatic or heterocyclic aldehyde (0·033 mole), and acetic anhydride (10 g.) was gently refluxed for 60 hr.; after cooling, the product was treated with a mixture of hydrochloric acid (15 c.c.) and water (15 c.c.), and the aldehyde in excess was removed by steam-distillation. The brown sticky resin which was precipitated on basification with aqueous sodium hydroxide was collected, dissolved in ethanol, and converted into a picrate or dipicrate. This was recrystallised and then decomposed with aqueous ammonia to give the base, which was taken up in benzene; the benzene solution was washed with water and dried (Na_2SO_4), the solvent was removed, and the residue recrystallised from ethanol. Yields ranged from 40% to 60%.

Benzacridinecarboxylic Acids.—A solution of 12-styrylbenz[*a*]acridine (1 g.) in acetone (60 c.c.) was refluxed for 2 hr. with potassium permanganate (1·25 g.); a further quantity of the oxidant (0·1 g.) was then added, and refluxing continued for 30 min. The solvent was distilled off, the residue treated with water, and sulphur dioxide was bubbled through the mixture to dissolve the manganese dioxide. The acid was filtered off and purified by dissolution in dilute aqueous sodium hydroxide and precipitation with acetic acid. Recrystallisation from ethanol afforded yellowish prisms (0·25 g.), m. p. 284° (decomp.) (Saftien [5] gave m. p. 284°) on slow heating, and instantaneously at 318°. Benz[*c*]acridine-7-carboxylic acid, prepared in the same way from 7-styrylbenz[*c*]acridine, formed yellowish prisms, m. p. 291°, from ethanol (Stollé *et al.*[5] gave m. p. 286°).

Spectra.—The ultraviolet absorption curves were determined in ethanol: 11-styrylbenz[*a*]acridine, $\lambda_{max.}$ 371 and 278 mμ (log ε 4·10 and 4·82); 11-styrylbenz[*c*]acridine, $\lambda_{max.}$ 369 (log ε 3·96) and 280, 290 mμ (log ε 4·68). The infrared spectra were taken in Nujol with a Unicam S.P. 100 apparatus, a sodium chloride prism, and a 600 lines/cm. grating. Nuclear magnetic resonance spectra were determined with a Varian A-60 (60 Mc.) apparatus with tetramethylsilane as internal reference.

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[6] Buu-Hoï and Lecocq, *Compt. rend.*, 1944, **218**, 792; Buu-Hoï, *J.*, 1946, 792.