1077. *Carcinogenic Nitrogen Compounds. Part XLIII.*[1] *Angular Benzacridines Bearing Electron-attracting Substituents.*

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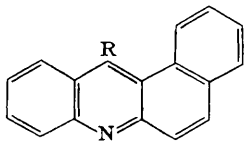
Benz[*a*]- and benz[*c*]-acridines bearing formyl, carboxyl, cyano, carboxyamide, and related electronegative groups, have been prepared for assessment of the influence of such substituents on their carcinogenicity.

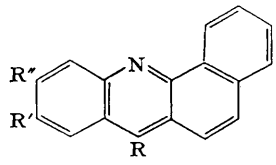
From theories which link the carcinogenic activity of polycyclic aromatic compounds with the π-electron densities in certain molecular areas, the introduction of electron-attracting

[1] Part XLII, N. P. Buu-Hoï, G. Saint-Ruf, and M. Dufour, *J.*, 1964, 5433.

substituents could be expected to be detrimental. However, in the class of aromatic hydrocarbons, substitution with the highly electronegative formyl,[2] acetyl,[3] and cyano-groups[4] has not infrequently led to quite active carcinogens, thus indicating a more complex relationship than a purely electronic one. As several of these carcinogens are 7-substituted benz[*a*]anthracenes, it was interesting to prepare similarly substituted derivatives of the isosteric benz[*a*]- (I) and benz[*c*]-acridines (II).



(I)



(II)

Benz[*c*]acridine-7-aldehyde was synthesised in good yield by oxidation, with selenium dioxide, of 7-methylbenz[*c*]acridine in xylene solution; a compound with the same structure but with a substantially different melting point was obtained by Porai-Koshits[5] in the reaction of *p*-nitrophenyldiazonium salts on 7-methylbenz[*c*]acridine and hydrolysis of the resulting *p*-nitrophenylhydrazone. Oxidation with selenium dioxide is limited to methyl groups in position 7, as 7,9-dimethyl- and 7,9,10-trimethyl-benz[*c*]acridine readily gave 7-formyl-9-methyl- and 7-formyl-9,10-dimethyl-benz[*c*]acridine, respectively; all three aldehydes reacted normally with reagents of the carbonyl group (hydroxylamine, thiosemicarbazide).

Benz[*c*]acridine-7-carboxylic acid was prepared by bromine-dehydrogenation of the 5,6-dihydro-compound (von Braun's tetrophan),[6] and this synthesis was extended to the 9-methyl and 9,10-dimethyl homologues of benz[*c*]acridine-7-carboxylic acid; these acids reacted with thionyl chloride to give the hydrochlorides of the corresponding acid chlorides which, on treatment with aqueous ammonia or dialkylamines, furnished the expected carboxyamides. In sharp contrast was the behaviour of benz[*a*]acridine-12-carboxylic acid: although this compound reacted normally with thionyl chloride to give the corresponding acid chloride, the latter showed a remarkable resistance towards ammoniolysis, ethanolysis, and hydrolysis; its hydrochloride, treated with concentrated aqueous ammonia, gave the free acid chloride (which could be recrystallised from ethanol without decomposition) in place of the expected carboxyamide. This carboxyamide could be obtained, in very low yields however, from the reaction of anhydrous ammonia on the acid chloride suspended in boiling methylene chloride; *NN*-dibutylbenz[*a*]acridine-12-carboxyamide was similarly obtained in the reaction of dibutylamine on the acid chloride in boiling xylene. The differences observed in the reactivity of the chlorides of benz[*c*]acridine-7-carboxylic acid and of benz[*a*]acridine-12-carboxylic acid might be due to the extreme steric encumbrance around the 12-position in the latter molecule.

7-Cyanobenz[*c*]acridine was prepared by dehydration of the corresponding amide by means of phosphorus oxychloride in the presence of pyridine,[7] a method which was also successfully applied to the synthesis of its homologues.

The biological tests are under way, and results will be reported elsewhere. The thiosemicarbazones described showed high *in vitro* tuberculostatic activity.

[2] M. J. Shear, J. Leiter, and A. Perrault, *J. Nat. Cancer Inst.*, 1940, **1**, 303; G. M. Badger, L. A. Elson, A. Haddow, C. L. Hewett, and A. M. Robinson, *Proc. Roy. Soc.*, 1941, *B*, **130**, 255.

[3] G. M. Badger, J. W. Cook, C. L. Hewett, E. L. Kennaway, N. M. Kennaway, and R. H. Martin, *Proc. Roy. Soc.*, 1942, *B*, **131**, 170.

[4] G. M. Badger, J. W. Cook, C. L. Hewett, E. L. Kennaway, N. M. Kennaway, R. H. Martin, and A. M. Robinson, *Proc. Roy. Soc.*, 1940, *B*, **129**, 439.

[5] A. E. Porai-Koshits and G. S. Ter-Sarkisyan, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1951, **601**, 771.

[6] J. von Braun and P. Wolff, *Ber.*, 1922, **55**, 3679.

[7] R. Delaby, G. Tsatsas, and X. Lusinchi, *Bull. Soc. chim. France*, 1955, 1609.

Experimental

Benz[c]*acridine-7-aldehyde* (II; R = CHO, R′ = R″ = H).—A solution of 7-methylbenz[*c*]acridine[8] (4 g.), m. p. 126°, in dry xylene (30 c.c.) was refluxed for 2 hr. with selenium dioxide (3·6 g.), the solvent distilled *in vacuo*, and the crude aldehyde thus obtained purified through its combination with sodium hydrogen sulphite. Decomposition of this with dilute hydrochloric acid, followed by basification, gave 7-formylbenz[*c*]acridine, which crystallised as pale yellow prisms (2·6 g.), m. p. 135° (from ethanol); (lit.,[8] 150°) (Found: C, 83·8; H, 4·5; N, 5·6. Calc. for $C_{18}H_{11}NO$: C, 84·0; H, 4·3; N, 5·5%). The *picrate* formed, from ethanol, orange needles, m. p. 171°, containing 1 molecule of ethanol (Found: N, 10·5. $C_{24}H_{14}N_4O_8,C_2H_5OH$ requires N, 10·5%). The *oxime* formed cream-coloured needles, m. p. 216° (from ethanol) (Found: N, 9·9. $C_{18}H_{12}N_2O$ requires N, 10·3%); the *thiosemicarbazone*, prepared by refluxing an ethanolic solution of the aldehyde with thiosemicarbazide for 2 hr., formed yellowish prisms, m. p. 298° (from ethanol) (Found: N, 17·1. $C_{19}H_{14}N_4S$ requires N, 17·0%). The selenium dioxide oxidation method was first applied to acridines by Monti[9] and by Buu-Hoï.[10]

7-*Formyl*-9-*methylbenz*[c]*acridine* (II; R = CHO, R′ = Me, R″ = H).—Similarly prepared, in 50% yield, from 7,9-dimethylbenz[*c*]acridine,[11] (m. p. 162°), this *aldehyde* formed yellow needles, m. p. 167° (from ethanol) (Found: C, 83·8; H, 5·0; N, 5·3. $C_{19}H_{13}NO$ requires C, 84·1; H, 4·8; N, 5·2%); *picrate*, orange-yellow needles, m. p. 161° (from ethanol) (Found: N, 10·8. $C_{25}H_{16}N_4O_8$ requires N, 11·2%); *oxime*, cream-coloured needles, m. p. 199° (from ethanol) (Found: N, 9·4. $C_{19}H_{14}N_2O$ requires N, 9·8%); *thiosemicarbazone*, yellow prisms, m. p. 290° (from ethanol) (Found: N, 15·9. $C_{20}H_{16}N_4S$ requires N, 15·7%).

7-*Formyl*-9,10-*dimethylbenz*[c]*acridine* (II; R = CHO, R′ = R″ = Me).—Obtained in 45% yield from 7,9,10-trimethylbenz[*c*]acridine[12] (m. p. 144°), this *aldehyde* formed pale yellow needles, m. p. 183° (from ethanol) (Found: C, 84·0; H, 5·5; N, 4·8. $C_{20}H_{15}NO$ requires C, 84·2; H, 5·3; N, 4·9%); *picrate*, yellow prisms, m. p. 170° (from ethanol) (Found: N, 10·7. $C_{26}H_{18}N_4O_8$ requires N, 10·9%); *oxime*, cream-coloured needles, m. p. 210° (from ethanol) (Found: N, 9·3. $C_{20}H_{16}N_2O$ requires N, 9·3%).

9-*Methylbenz*[c]*acridine-7-carboxylic Acid* (II; R = CO_2H, R′ = Me, R″ = H).—5,6-Dihydro-9-methylbenz[*c*]acridine-7-carboxylic acid[6] (2·9 g.; m. p. 297°; lit.,[6] 298°) was treated with bromine (4 g.) in boiling acetic acid for 4 hr., and the precipitate formed after cooling and dilution with water was collected, dissolved in 20% aqueous sodium hydroxide, and reprecipitated with acetic acid; the *acid* obtained crystallised as yellowish prisms (2·5 g.), m. p. 285° (from ethanol) (Found: C, 79·1; H, 4·5; N, 4·9. $C_{19}H_{13}NO_2$ requires C, 79·4; H, 4·6; N, 4·9%).

5,6-*Dihydro*-9,10-*dimethylbenz*[c]*acridine-7-carboxylic Acid*.—A solution of 5,6-dimethylisatin (17·5 g.), 1-tetralone (15 g.), and potassium hydroxide (16·8 g.) in ethanol (100 c.c.) was gently refluxed for 24 hr., the solvent distilled *in vacuo*, the residue taken up in water, and the aqueous solution extracted with ether and acidified with acetic acid. The precipitate formed cream-coloured prisms (24 g.), m. p. 328° (decomp. > 290°) (from acetic acid) (Found: C, 79·0; H, 6·0; N, 4·4. $C_{20}H_{17}NO_2$ requires C, 79·2; H, 5·7; N, 4·6%). 9,10-*Dimethylbenz*[c]*acridine-7-carboxylic acid* (II; R = CO_2H, R′ = R″ = Me), obtained by bromine-dehydrogenation of the above, formed yellowish microneedles, m. p. 340° (decomp. > 320°) (from ethanol) (Found: C, 79·4; H, 5·2; N, 4·7. $C_{20}H_{15}NO_2$ requires C, 79·7; H, 5·0; N, 4·7%).

Reaction of the Benz[c]*acridine-7-carboxylic Acids with Thionyl Chloride*.—A mixture of carefully dried, finely powdered benz[*c*]acridine-7-carboxylic acid (10 g.) and thionyl chloride (20 g.) was refluxed until solution was obtained (1 hr.), the excess of thionyl chloride was then distilled off *in vacuo*, and the solid residue washed with anhydrous ether; the hygroscopic, cream-coloured *acid chloride hydrochloride* thus obtained in almost theoretical yield melted sharply at 161° (Found: N, 4·3. $C_{18}H_{10}Cl_2NO,HCl$ requires N, 4·3%). 9-*Methylbenz*[c]*acridine-7-carboxylic acid chloride hydrochloride*, similarly prepared, was a pale yellow, microcrystalline powder, m. p. 128° (Found: N, 4·2. $C_{19}H_{13}Cl_2NO$ requires N, 4·1%); 9,10-*dimethylbenz*[c]*acridine-7-carboxylic acid chloride hydrochloride*, yellow microprisms, m. p. 143° (Found: N, 3·8. $C_{20}H_{12}Cl_2NO$ requires N, 3·9%). All these acid chlorides readily underwent hydrolysis on contact with water.

[8] Y. Postovskii and B. N. Lundin, *J. Gen. Chem.* (*U.S.S.R.*), 1940, **10**, 71.
[9] L. Monti, *Atti Accad. naz. Lincei, Rend. Classe Sci. fis. mat. nat.*, 1936, **24**, 145.
[10] N. P. Buu-Hoï and J. Lecocq, *Rec. Trav. chim.*, 1945, **64**, 250.
[11] N. P. Buu-Hoï and J. Lecocq, *Compt. rend.*, 1944, **218**, 792.
[12] N. P. Buu-Hoï, *J.*, 1949, 670.

Benz[c]*acridine-7-carboxyamide*.—This compound, prepared in 91% yield by shaking the finely powdered acid chloride hydrochloride with concentrated aqueous ammonia at 0°, formed yellowish prisms, m. p. 234—235° (from ethanol) (Found: N, 10·4. Calc. for $C_{18}H_{12}N_2O$: N, 10·3%); von Braun,[13] who prepared it in a different way, gave m. p. 224°. Another amidation procedure used consisted of running anhydrous ammonia through a suspension of the acid chloride hydrochloride in methylene chloride. The amide formed a *picrate*, bright yellow prisms, m. p. 230° (decomp. > 200°) (from ethanol) (Found: N, 13·7. $C_{24}H_{15}N_4O_8$ requires N, 14·0%); *hydrochloride* (prepared in ether), pale yellow microneedles, m. p. 227° (Found: Cl, 11·2. $C_{18}H_{13}ClN_2O$ requires Cl, 11·5%). The other carboxyamides were prepared in the same way and with similar yields. The amides derived from dimethylamine were obtained in 70% yield

New benz[*c*]acridine-7-carboxyamides.

Substituents on: Nucleus	Amide nitrogen	M. p.	Formula	Found (%) C	H	N	Required (%) C	H	N
None	Dimethyl	178°	$C_{20}H_{16}N_2O$	79·6	5·6	9·3	80·0	5·4	9·3
Picrate		180	$C_{26}H_{19}N_5O_8$	—	—	13·5	—	—	13·2
None	Diethyl	113	$C_{22}H_{20}N_2O$	80·0	6·3	8·5	80·5	6·1	8·5
Picrate		172	$C_{28}H_{23}N_5O_8$	—	—	12·4	—	—	12·6
7-Methyl	None	248	$C_{19}H_{14}N_2O$	79·5	5·2	9·8	79·7	4·9	9·8
Picrate		248	$C_{25}H_{17}N_5O_8$	—	—	13·5	—	—	13·6
Hydrochloride		199	$C_{19}H_{15}ClN_2O$	—	—	Cl, 11·3	—	—	Cl, 11·0
7-Methyl	Dimethyl	183	$C_{21}H_{18}N_2O$	80·0	6·1	8·7	80·2	5·8	8·9
Picrate		184	$C_{27}H_{21}N_5O_8$	—	—	12·9	—	—	12·9
Hydrochloride		131	$C_{21}H_{19}ClN_2O$	—	—	Cl, 10·1	—	—	Cl, 10·1
7-Methyl	Diethyl	130	$C_{23}H_{22}N_2O$	80·5	6·5	8·3	80·7	6·4	8·2
Picrate		180	$C_{29}H_{25}N_5O_8$	—	—	12·4	—	—	12·2
Hydrochloride		143	$C_{23}H_{23}ClN_2O$	—	—	Cl, 9·2	—	—	Cl, 9·4
9,10-Dimethyl	None	288	$C_{20}H_{16}N_2O$	79·9	5·4	9·3	80·0	5·3	9·3
Picrate		270	$C_{26}H_{19}N_5O_8$	—	—	13·2	—	—	13·2
9,10-Dimethyl	Dimethyl	200	$C_{22}H_{20}N_2O$	80·1	6·4	8·5	80·5	6·1	8·5
Picrate		212	$C_{28}H_{23}N_5O_8$	—	—	12·7	—	—	12·6
9,10-Dimethyl	Diethyl	160	$C_{24}H_{24}N_2O$	80·7	7·2	7·8	80·9	6·8	7·9
Picrate		224	$C_{30}H_{27}N_5O_8$	—	—	12·1	—	—	12·0

by treating a suspension of the corresponding acid chloride hydrochloride (2 g.) in methylene chloride with dimethylamine (1 g.) at 0°, distillation of the solvent, and crystallisation of the residue from cyclohexane; the amides derived from diethylamine were prepared, in similar yields, by refluxing for 1 hr. a suspension of the acid chloride hydrochloride in benzene with diethylamine, and crystallisation of the product from cyclohexane. These various new amides are listed in the Table, together with their picrates (which formed bright yellow prisms from ethanol) and their hydrochlorides (pale yellow, prepared in anhydrous ether).

7-*Cyanobenz*[c]*acridine* (II; R = CN, R′ = R″ = H).—A solution of benz[*c*]acridine-7-carboxyamide (3 g.) in anhydrous pyridine (10 c.c.) was treated with phosphorus oxychloride (0·8 g.) and refluxed for 1 hr.; after cooling, dilution with water, and neutralisation with aqueous sodium hydrogen carbonate, the precipitate was recrystallised from ethanol, giving straw-coloured needles (1·7 g.), m. p. 190° (Found: C, 85·1; H, 4·0; N, 11·0. $C_{18}H_{10}N_2$ requires C, 85·0; H, 4·0; N, 11·0%). The following nitriles were similarly prepared, in 60% yield: 7-*cyano*-9-*methylbenz*[c]-*acridine* (II; R = CN, R′ = Me, R″ = H), pale yellow needles, m. p. 208° (from ethanol–benzene) (Found: C, 84·7; H, 4·8; N, 10·5. $C_{19}H_{12}N_2$ requires C, 85·1; H, 4·5; N, 10·4%); 7-*cyano*-9,10-*dimethylbenz*[c]*acridine* (II; R = CN, R′ = R″ = Me), straw-coloured needles, m. p. 193° (from ethanol) (Found: C, 84·8; H, 5·4; N, 9·8. $C_{20}H_{14}N_2$ requires C, 85·1; H, 5·0; N, 9·9%).

Reactions of Benz[a]*acridine-12-carboxylic Acid* (I; R = CO_2H).—This acid was prepared in 60% yield, by condensing naphtho[2,1-*b*]furan-1,2-dione[14] with aniline in boiling acetic acid, and purified *via* its sodium salt; the ultraviolet absorption spectrum of this latter, taken in water at pH = 10 [$\lambda_{max.}$ 239·5 (log ε 4·16), 277·2 (log ε 4·63), 348 (log ε 3·54), 363 (log ε 3·62), and 383 mμ (log ε 3·54)] closely resembled that of benz[*a*]acridine. Heating the acid above its m. p. furnished benz[*a*]acridine, m. p. 132°.

To this acid (2 g.), finely powdered and dried at 120°, thionyl chloride (4 g.) was added dropwise, and the mixture heated for 1 hr. on a water-bath; the thionyl chloride in excess was distilled *in vacuo* and the residue ground with anhydrous benzene, leaving *benz*[a]*acridine*-12-

[13] J. von Braun, *Annalen*, 1927, **451**, 19.
[14] K. Saftien, *Ber.*, 1925, **58**, 1960.

carboxylic acid chloride hydrochloride, as a yellow, microcrystalline powder (2 g.), m. p. 155° (Found: N, 4·4. $C_{18}H_{11}Cl_2NO$ requires N, 4·3%). Treatment of this compound with concentrated aqueous ammonia, either at room temperature or at boiling point, did not give the amide; instead, *benz*[a]*acridine*-12-*carboxylic acid chloride* (I; R = COCl) was obtained, crystallising without decomposition from boiling ethanol, as yellowish prisms, m. p. 168° (Found: C, 74·1; H, 3·4. $C_{18}H_{10}ClNO$ requires C, 74·2; H, 3·4%). The action of hydrogen chloride on this compound regenerated the foregoing hydrochloride, m. p. 155°; this compound resisted hydrolysis and remained unchanged after 10 min. in boiling water. *Benz*[a]*acridine*-12-*carboxyamide* (I; R = $CONH_2$) was obtained in 25% yield by bubbling anhydrous ammonia for 30 min. into a stirred suspension of the foregoing acid chloride in boiling methylene chloride; after cooling, filtration, and evaporation of the solvent from the filtrate, the residue was recrystallised from ethanol, giving pale yellow needles, m. p. 278° (sublim. > 245°) (Found: C, 78·9; H, 4·6. $C_{18}H_{12}N_2O$ requires C, 79·4; H, 4·4%); *picrate*, yellow needles, m. p. 216° (from ethanol) (Found: N, 13·4%). NN-*Dibutylbenz*[a]*acridine*-12-*carboxyamide* (I; R = $CONBu_2$), prepared by refluxing for 4 hr. a xylene solution of the acid chloride with an excess of dibutylamine, formed cream-coloured needles, m. p. 104° (from cyclohexane) (Found: C, 81·2; H, 7·5; N, 7·4. $C_{26}H_{28}N_2O$ requires C, 81·2; H, 7·3; N, 7·3%); picrate, yellow needles, m. p. 196° (from ethanol).

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