[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

POTENTIAL NITROGEN-HETEROCYCLE CARCINOGENS. XII. 9-ETHYLCARBAZOLE-3-ALDEHYDE AND ITS DERIVATIVES[1]

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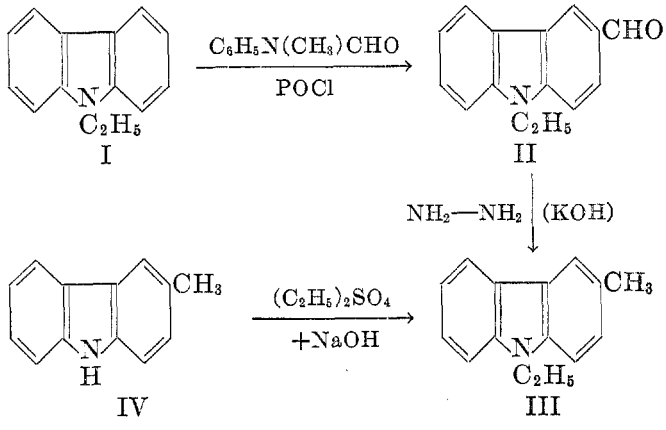
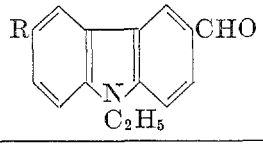
Received February 19, 1951

The aldehyde synthesis with N-methylformanilide and phosphorus oxychloride so far has been successfully applied to phenyl and naphthyl ethers, dialkylanilines, polycyclic hydrocarbons (1), and heterocyclic compounds with labile hydrogen atoms, such as thiophene and its homologs (2).

The high degree of reactivity of N-alkylcarbazoles as shown by their ready halogenation and their usefulness in Friedel-Crafts reactions (3) led us to expect that this group of compounds would undergo the N-methylformanilide aldehyde synthesis also. This was found to be so, and an aldehyde was obtained in excellent yield from 9-ethylcarbazole (I). This aldehyde proved to be 9-ethylcarbazole-3-aldehyde (II) since a Wolff-Kishner reduction gave 3-methyl-9-ethylcarbazole (III); the latter compound was identical with the N-ethylation product of 3-methylcarbazole (IV).



The N-methylformanilide reaction is also possible in this series when the 3-position is blocked by an alkyl group. Thus, 3-methyl-9-ethylcarbazole readily gave 6-methyl-9-ethylcarbazole-3-aldehyde (V), whose constitution was proved by a Wolff-Kishner reduction to 3,6-dimethyl-9-ethylcarbazole, a compound identical with that obtained by N-ethylation of the known 3,6-dimethylcarbazole (4).

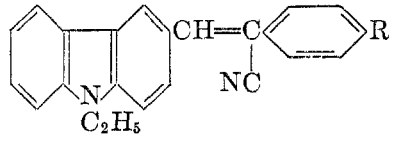


V R = CH_3
VI R = Br
VII R = NO_2

[1] Paper XI in this series: Buu-Hoï and Royer, *J. Org. Chem.*, **16**, August (1951).

9-Ethylcarbazole-3-aldehyde lent itself readily to substitution: with bromine in acetic acid, 6-bromo-9-ethylcarbazole-3-aldehyde (VI) was obtained, and with nitric acid in acetic anhydride—acetic acid medium, 6-nitro-9-ethylcarbazole-3-aldehyde (VII) was prepared, both in excellent yield.

Besides their usefulness for the synthesis of polymethylcarbazoles otherwise difficult of access, carbazole aldehydes lend themselves to the preparation of several compounds of varied interest in biological research. For example, the condensation of 9-ethylcarbazole-3-aldehyde with phenylacetonitriles in the presence of alkaline catalysts readily gave a series of α-aryl-β-(9-ethylcarbazol-3-yl)acrylonitriles, whose stilbene structure makes them of interest in cancer

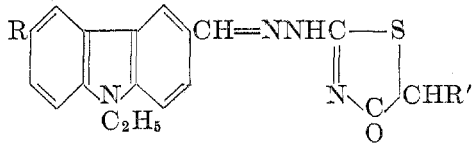


VIII R = F
IX R = Cl
X R = Br
XI R = I

research (5). In view of the increased toxicity generally shown by organic molecules upon the introduction of halogen atoms, we have prepared α-*p*-fluorophenyl- (VIII), α-*p*-chlorophenyl- (IX), α-*p*-bromophenyl- (X), and α-*p*-iodophenyl-β-(9-ethylcarbazol-3-yl)acrylonitrile (XI). These substances, which might also be of interest as potential antagonists of estrogens, are undergoing biological investigation in this institute under Professor A. Lacassagne.

Another aspect of the biological interest of carbazole aldehydes lies in the potential antitubercular properties of their thiosemicarbazones. It is known from previous studies (6) that the antitubercular properties of thiosemicarbazones depend largely on the molecular structure of the parent aldehyde or ketone. The thiosemicarbazones of 9-ethylcarbazole-3-aldehyde and of 6-methyl-9-ethylcarbazole-3-aldehyde have now been prepared, and were found to be highly active *in vitro* (one part in ten million) against *Mycobacterium tuberculosis*, despite their large molecular weight. The thiosemicarbazones of 6-bromo- and 6-nitro-9-ethylcarbazole-3-aldehyde were less effective. Details of this bacteriological work, performed by Dr. M. Welsch (University of Liège), are being published elsewhere.

The Cattelain-Chabrier condensation (7) of these thiosemicarbazones with α-halogenated fatty acids led easily to the 4-keto-2-thiazolinylhydrazones of



XII

the corresponding carbazole aldehydes. These substances, represented by the general formula XII, are listed in Table I; they are less tuberculostatic than the parent thiosemicarbazones.

Acknowledgement. This work was financially aided by the U. S. Public Health

Service (Federal Security Agency); the authors express their gratitude to the authorities concerned. Our thanks are also due to "La Société Belge de l'Azote" for help with some biological assays.

EXPERIMENTAL[2]

9-Ethylcarbazole-3-aldehyde (II). A mixture of 100 g. of redistilled N-ethylcarbazole, 76 g. of N-methylformanilide, 76 g. of phosphorus oxychloride, and 100 ml. of *o*-dichlorobenzene was heated for four hours on a steam-bath at 90–95°. After cooling, a solution of 300 g. of crystalline sodium acetate in 600 ml. of water was added, and the solvent and N-methylaniline were removed by steam-distillation. The residual oil was taken up in toluene, the solution dried over sodium sulfate, the solvent removed, and the residue vacuum-fractionated. Yield, 65 g. of the aldehyde, b.p. about 254–255°/15 mm., and crystallizing from methanol in fine shiny, colorless needles, m.p. 94°. Since 35 g. of N-ethylcarbazole was recovered in the forerun, the adjusted yield was 87.4%.

Anal. Calc'd for $C_{15}H_{13}NO$: C, 80.7; H, 5.8.
Found: C, 80.5; H, 5.9.

The corresponding *thiosemicarbazone* crystallized from ethanol or ethyl acetate in fine shiny, pale yellow needles, melting at about 228° with decomposition.

Anal. Calc'd for $C_{16}H_{16}N_4S$: N, 18.9. Found: N, 18.6.

3-Methyl-9-ethylcarbazole (III). A mixture of 50 g. of the foregoing aldehyde, 50 g. of 85% hydrazine hydrate, 50 g. of potassium hydroxide, and 350 ml. of diethylene glycol (8) was cautiously refluxed with removal of water until the temperature reached 195–200°, refluxing then being continued for a further hour. After cooling, the mixture was diluted with water and extracted several times with benzene. The benzene solution was washed with dilute hydrochloric acid, then with water, and dried over sodium sulfate. After removal of the solvent, the residue was vacuum-distilled, giving 37 g. of 3-methyl-9-ethylcarbazole, b.p. 205–207°/13 mm., crystallizing from methanol in clumps of long silky, colorless needles, m.p. 45°. For comparison, 3-methylcarbazole, prepared according to the literature (9) and dissolved in an acetone solution of sodium hydroxide, was alkylated with ethyl sulfate in the usual way. The ethylation product was identical with the 3-methyl-9-ethylcarbazole prepared by the previous method.

Anal. Calc'd for $C_{15}H_{15}N$: C, 86.1; H, 7.2.
Found: C, 86.0; H, 7.1.

6-Bromo-9-ethylcarbazole-3-aldehyde (VI). An ice-cooled acetic acid solution of 11 g. of 9-ethylcarbazole-3-aldehyde was treated with 8 g. of bromine (dissolved in acetic acid) in small portions with stirring. After 10 minutes, the reaction product was poured into water, and the precipitate recrystallized from ethanol. Yield, 98% of a product crystallizing from ethanol in colorless needles, m.p. 136°.

Anal. Calc'd for $C_{15}H_{12}BrNO$: C, 59.6; H, 4.0.
Found: C, 59.5; H, 4.2.

The corresponding *thiosemicarbazone* formed from a mixture of ethanol and benzene fine, almost colorless needles melting with decomposition at about 228°.

Anal. Calc'd for $C_{16}H_{15}BrN_4S$: C, 51.2; H, 4.0.
Found: C, 50.9; H, 4.2.

6-Nitro-9-ethylcarbazole-3-aldehyde (VII). To an ice-cooled solution of 9 g. of 9-ethylcarbazole-3-aldehyde in 30 ml. of acetic anhydride, a solution of 3 g. of fuming nitric acid (*d.* 1.49) in 20 ml. of acetic acid was added dropwise with stirring. The mixture was left for a further 15 minutes in the cold, and then poured into water. The precipitate formed (98% yield) was collected and thoroughly washed with water; it was recrystallized from acetic acid in long shiny, yellow sublimable needles, m.p. 248°.

Anal. Calc'd for $C_{15}H_{12}N_2O_3$: C, 67.1; H, 4.5.
Found: C, 66.8; H, 4.4.

[2] All melting points are uncorrected and were taken with a Maquenne block.

The *thiosemicarbazone*, crystallized from xylene or acetic acid, formed fine yellow prisms melting at about 237° with decomposition.

Anal. Calc'd for $C_{16}H_{15}N_5O_2S$: C, 56.2; H, 4.4.

Found: C, 56.0; H, 4.3.

6-Methyl-9-ethylcarbazole-3-aldehyde (V). The reaction between 25 g. of 3-methyl-9-ethylcarbazole, 20 g. of N-methylformanilide, and 20 g. of phosphorus oxychloride was performed in the usual way but with toluene (150 ml.) as solvent. Yield, 17 g. of an aldehyde, b.p. 266–268°/15 mm., crystallizing from methanol in almost colorless needles, m.p. 91°.

TABLE I

4-KETO-2-THIAZOLINYLHYDRAZONES (XII) OF CARBAZOLE ALDEHYDES

RADICALS R AND R′	FORMULA	M.P., °C.	ANALYSES			
			Calc'd		Found	
			C	H	C	H
R = R′ = H	$C_{18}H_{16}N_4OS$	291	64.3	4.8	64.0	4.7
R = H, R′ = C_2H_5	$C_{20}H_{20}N_4OS$	265	65.9	5.5	65.5	5.6
R = H, R′ = *n*-C_3H_7	$C_{21}H_{22}N_4OS$	238	66.7	5.8	66.6	5.6
R = H, R′ = *n*-C_4H_9	$C_{22}H_{24}N_4OS$	227	67.3	6.1	67.1	6.0
R = H, R′ = *n*-$C_{14}H_{29}$	$C_{32}H_{44}N_4OS$	152	72.2	8.3	71.9	8.1
R = H, R′ = *n*-$C_{16}H_{33}$	$C_{34}H_{48}N_4OS$	145	72.8	8.6	72.6	8.4
R = CH_3, R′ = H	$C_{19}H_{18}N_4OS$	286	65.1	5.1	65.0	5.4
R = CH_3, R′ = C_2H_5	$C_{21}H_{22}N_4OS$	245	66.7	5.8	66.4	6.0
R = CH_3, R′ = *n*-C_3H_7	$C_{22}H_{24}N_4OS$	244	67.3	6.1	67.0	6.2
R = CH_3, R′ = *n*-C_4H_9	$C_{23}H_{26}N_4OS$	226	68.0	6.4	67.8	6.6
R = CH_3, R′ = *n*-$C_{14}H_{29}$	$C_{33}H_{46}N_4OS$	168	72.5	8.4	72.4	8.6
R = CH_3, R′ = *n*-$C_{16}H_{33}$	$C_{35}H_{50}N_4OS$	162	73.2	8.7	73.0	8.5
R = Br, R′ = H	$C_{18}H_{15}BrN_4OS$	320	52.0	3.6	51.7	3.8
R = Br, R′ = C_2H_5	$C_{20}H_{19}BrN_4OS$	306	54.2	4.3	54.0	4.1
R = Br, R′ = *n*-C_4H_9	$C_{22}H_{23}BrN_4OS$	268	56.0	4.9	55.8	4.8
R = Br, R′ = *n*-$C_{14}H_{29}$	$C_{32}H_{43}BrN_4OS$	208	62.8	7.0	62.7	7.1
R = Br, R′ = *n*-$C_{16}H_{33}$	$C_{34}H_{47}BrN_4OS$	182	63.8	7.3	63.5	7.2
R = NO_2, R′ = H	$C_{18}H_{15}N_5O_3S$	340	56.7	3.9	56.3	4.0
R = NO_2, R′ = C_2H_5	$C_{20}H_{19}N_5O_3S$	322	58.7	4.6	58.6	4.4
R = NO_2, R′ = *n*-C_4H_9	$C_{22}H_{23}N_5O_3S$	266	60.4	5.3	60.0	5.2
R = NO_2, R′ = *n*-$C_{16}H_{33}$	$C_{34}H_{47}N_5O_3S$	225	67.4	7.8	67.2	7.8

Anal. Calc'd for $C_{16}H_{15}NO$: C, 81.0; H, 6.3.

Found: C, 80.9; H, 6.5.

The *thiosemicarbazone* formed from ethanol fine cream needles, melting at about 199°.

Anal. Calc'd for $C_{17}H_{18}N_4S$: N, 18.1. Found: N, 17.8.

3,6-Dimethyl-9-ethylcarbazole. A mixture of 4 g. of 6-methyl-9-ethylcarbazole, 4 g. of 85% hydrazine hydrate, 4 g. of potassium hydroxide, and 50 ml. of diethylene glycol was treated as for the preparation of 3-methyl-9-ethylcarbazole. The yield was 3.5 g. of a product crystallizing from methanol in shiny colorless leaflets, m.p. 67°.

Anal. Calc'd for $C_{16}H_{17}N$: C, 86.1; H, 7.6.

Found: C, 86.0; H, 7.8.

The *alkylation* of 3,6-dimethylcarbazole in alkaline solution with ethyl sulfate gave the same product.

α-p-Fluorophenyl-β-(9-ethylcarbazol-3-yl)acrylonitrile (VIII). *p*-Fluorophenylacetonitrile was prepared from *p*-fluorobenzyl chloride and potassium cyanide in acetone. Equimolec-

ular amounts of this nitrile and 9-ethylcarbazole-3-aldehyde in warm ethanol were shaken with a few drops of 30% aqueous potassium hydroxide. There was an immediate separation of an oil which quickly solidified; after recrystallization from a mixture of ethanol and benzene, fine greenish yellow needles, m.p. 146°, were obtained, which gave with sulfuric acid a violet-brown coloration.

Anal. Calc'd for $C_{23}H_{17}FN_2$: C, 81.2; H, 5.0.
Found: C, 81.2; H, 5.1.

α-p-Chlorophenyl-β-(9-ethylcarbazol-3-yl)acrylonitrile (IX) was similarly prepared from *p*-chlorophenylacetonitrile and 9-ethylcarbazole-3-aldehyde; it formed from a mixture of ethanol and benzene fine greenish needles, m.p. 157°.

Anal. Calc'd for $C_{23}H_{17}ClN_2$: C, 77.4; H, 4.8.
Found: C, 77.1; H, 5.0.

α-p-Bromophenyl-β-(9-ethylcarbazol-3-yl)acrylonitrile (X) crystallized from a mixture of ethanol and benzene as fine, pale yellow needles, m.p. 157°.

Anal. Calc'd for $C_{23}H_{17}BrN_2$: C, 68.8; H, 4.2.
Found: C, 68.5; H, 4.1.

α-p-Iodophenyl-β-(9-ethylcarbazol-3-yl)acrylonitrile (XI) crystallized from a mixture of ethanol and benzene in pale yellow needles, m.p. 161°, giving an orange coloration with sulfuric acid.

Anal. Calc'd for $C_{23}H_{17}IN_2$: C, 61.6; H, 3.8.
Found: C, 61.4; H, 3.6.

The *p*-fluoro-, *p*-chloro-, *p*-bromo-, and *p*-iodo-phenylacetonitriles used were prepared from potassium cyanide and *p*-fluoro-, *p*-chloro-, *p*-bromo-, and *p*-iodo-benzyl chlorides, which were obtained by chloromethylation of fluoro-, chloro-, bromo-, and iodo-benzene (10).

Preparation of 4-keto-2-thiazolinylhydrazones of carbazole aldehydes. A suspension in acetic acid or ethanol of the thiosemicarbazone of the corresponding aldehyde was refluxed for six hours with the theoretical amount of an α-halogenated fatty acid in the presence of sodium acetate; after cooling, the precipitate was collected and recrystallized several times from acetic acid or toluene. The 4-keto-2-thiazolinylhydrazones thus obtained were extremely difficult to burn, and correct analyses could be obtained only when large excesses of oxidizing agents were used.

The α-halogenated acids used were: chloroacetic, α-bromo-*n*-butyric, α-bromo-*n*-valeric, α-bromocaproic, α-bromopalmitic, and α-bromostearic acids.

SUMMARY

1. The N-methylformanilide aldehyde synthesis has been successfully applied to the carbazole series, and several aldehydes derived from N-ethylcarbazole are described.

2. A number of α-aryl-β-carbazolylacrylonitriles have been prepared for cancer studies.

3. Several thiosemicarbazones and 4-keto-2-thiazolinylhydrazones of various carbazole aldehydes bearing potential antitubercular properties have been synthesized; two thiosemicarbazones showed outstanding tuberculostatic activity *in vitro*.

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