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

SOME ANTHRACENE DERIVATIVES OF POTENTIAL BIOLOGICAL INTEREST

NG.PH. BUU-HOÏ AND NG. HOÁN

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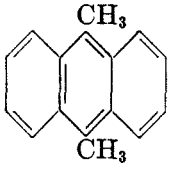
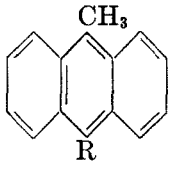
Apart from the fact that the anthracene skeleton is present in the molecule of most carcinogenic polycyclic hydrocarbons (1), some simple anthracene derivatives have also been found to be carcinogenic. Such is the case of 9,10-dimethylanthracene (I), which elicits skin epitheliomas in mice by painting (2), and of 2-anthramine, which gives hepatomas in mice by injection (3) and various carcinomatas in rats by painting (4). These results warrant a broad investigation into the synthesis of anthracene derivatives of possible biological interest.



I



II. R = H
III. R = CHO

9,10-Dimethylanthracene, a key hydrocarbon, has now been conveniently prepared in quantity by the following sequence of reactions:

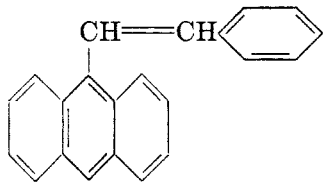
(a) formylation of anthracene to 9-anthraldehyde with N-methylformanilide (5);

(b) reduction of 9-anthraldehyde to 9-methylanthracene (II) by the Wolff-Kishner method as modified by Huang-Minlon (6);

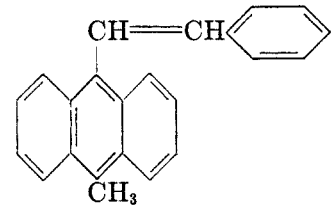
(c) repetition of these reactions upon 9-methylanthracene to give 9-methyl-10-anthraldehyde (III) and 9,10-dimethylanthracene respectively. This four-step synthesis is nevertheless far superior to those already recorded in the literature (7).

According to Pinck's theory of chemical carcinogenesis (8), the action of tumor-producing compounds, especially those bearing methyl or methylene groups in their molecules, may involve biochemical conversion into ethylenic compounds which then react with certain cellular constituents through their external double bonds. This theory suggests the preparation and testing of more ethylenic compounds for carcinogenic properties, especially those of the stilbene type, containing a polycyclic radical such as the anthracene one. The reaction of benzylmagnesium chloride with 9-anthraldehyde readily gave the expected secondary alcohol (benzyl-9-anthrylcarbinol), which readily lost water on vacuum-distillation to give a mixture of two isomeric styrylanthracenes (IV). By analogy with stilbene, the lower-melting isomer could be tentatively assigned the *cis*-structure and the higher-melting one the *trans*-structure, the former isomer being formed predominantly. However, when a similar reaction was

carried out with 9-methyl-10-anthraldehyde and benzylmagnesium chloride, only one 9-methyl-10-styrylanthracene (V) was obtained. The latter compound is of particular interest as both *meso*-positions are substituted, a circumstance generally favorable to carcinogenicity.

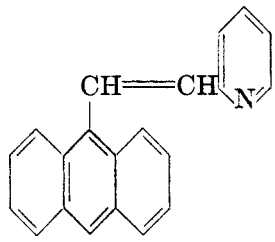


IV

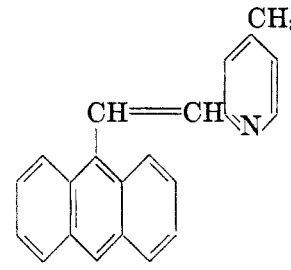


V

Similar compounds in the pyridine group, and related to stilbazole, were α-(9-anthryl)-β-(2-pyridyl)ethylene (VI) and α-(9-anthryl)-β-(4-methyl-2-pyridyl)ethylene (VII), which were readily prepared through the condensation of 9-anthraldehyde with α-picoline and 2,4-lutidine in the presence of acetic anhydride.

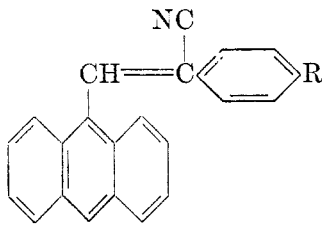


VI



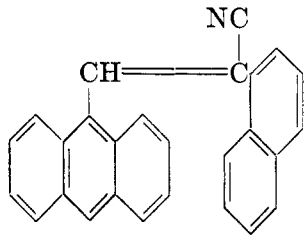
VII

Although 9-anthraldehyde does not form an addition compound with sodium bisulfite (9), a circumstance suggesting steric hindrance around the aldehyde group, this compound reacted easily with the methylene group of arylacetonitriles ($ArCH_2CN$) in the presence of alkaline catalysts to give α-aryl-β-(9-anthryl)acrylonitriles. Thus there was obtained with benzyl cyanide α-phenyl-

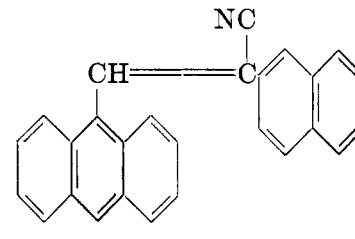


VIII, R = H
IX, R = CH_3
X, R = F
XI, R = Cl
XII, R = Br
XIII, R = I
XIV, R = OCH_3
XV, R = NO_2

β-(9-anthryl)acrylonitrile (VIII), and with seven of its *para*-substituted derivatives the corresponding acrylonitriles (IX to XV). This reaction could be extended to the 1- and 2-naphthylacetonitriles, to give α-(1-naphthyl)- (XVI) and α-(2-naphthyl)-β-(9-anthryl)acrylonitrile (XVII), and even to heterocyclic



XVI



XVII

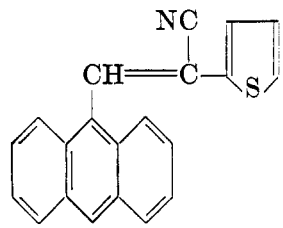
compounds such as 2-thienylacetonitrile and 2,5-dimethyl-3-thienylacetonitrile

TABLE I

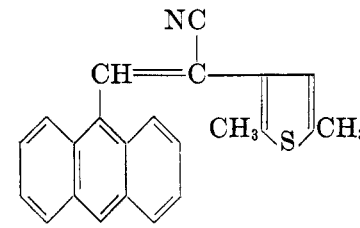
α-ARYL-β-(9-ANTHRYL)ACRYLONITRILES

SUBSTANCES	α-RADICAL	FORMULA	M.P., °C.	ANALYSES			
				Calc'd		Found	
				C	H	C	H
VIII	Phenyl	$C_{23}H_{15}N$	163	90.5	4.9	90.3	5.0
IX	*p*-Tolyl	$C_{24}H_{17}N$	212	90.3	5.3	90.2	5.4
X	*p*-Fluorophenyl	$C_{23}H_{14}FN$	206	85.4	4.3	85.2	4.1
XI	*p*-Chlorophenyl	$C_{23}H_{14}ClN$	213	81.3	4.1	81.2	4.2
XII	*p*-Bromophenyl	$C_{23}H_{14}BrN$	223	71.8	3.6	71.6	3.6
XIII	*p*-Iodophenyl	$C_{23}H_{14}IN$	225	64.0	3.2	63.8	3.4
XIV	*p*-Methoxyphenyl	$C_{24}H_{17}NO$	212	85.9	5.0	85.6	5.1
XV	*p*-Nitrophenyl	$C_{23}H_{14}N_2O_2$	281	78.8	4.0	78.7	4.2
XVI	1-Naphthyl	$C_{27}H_{17}N$	219	91.3	4.8	91.2	4.8
XVII	2-Naphthyl	$C_{27}H_{17}N$	216	91.3	4.8	91.1	4.7
XVIII	2-Thienyl	$C_{21}H_{13}NS$	203	81.0	4.2	81.0	4.2
XIX	2,5-Dimethyl-3-thienyl	$C_{23}H_{17}NS$	210	81.4	5.0	81.2	5.2

to give α-(2-thienyl)- (XVIII) and α-(2,5-dimethyl-3-thienyl)-β-(9-anthryl)acrylonitrile (XIX).

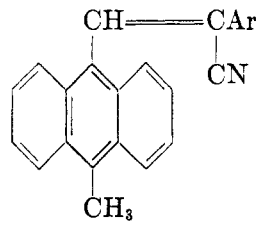


XVIII

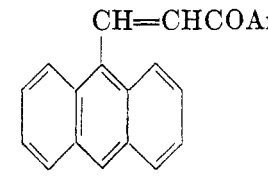


XIX

A similar series of α-aryl-β-(9-methyl-10-anthryl)acrylonitriles of the general formula (XX) was also readily obtained from 9-methyl-10-anthraldehyde with various arylacetonitriles and with 2-thienylacetonitrile, and these are listed along with the former acrylonitriles in Tables I and II. These substances are derived from the basic hydrocarbons (IV) and (V), and like them, give intense halochromic colorations with sulfuric acid.



XX



XXI

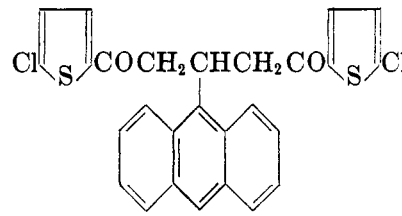
Another class of highly *meso*-conjugated anthracene compounds is comprised of the chalkones of the general formula XXI, obtained from 9-anthraldehyde with various acetophenones in the presence of alkaline catalysts. In the thiophene series, an anomaly was observed inasmuch as with 2-acetothienone and

TABLE II

α-ARYL-β-(9-METHYL-10-ANTHRYL)ACRYLONITRILES (XX)

α-RADICAL	FORMULA	M.P., °C.	ANALYSES			
			Calc'd		Found	
			C	H	C	H
Phenyl	$C_{24}H_{17}N$	253	90.3	5.3	90.2	5.4
p-Tolyl	$C_{25}H_{19}N$	200	90.1	5.7	89.8	5.8
p-Chlorophenyl	$C_{24}H_{16}ClN$	240	81.4	4.5	81.2	4.7
p-Bromophenyl	$C_{24}H_{16}BrN$	231	72.3	4.0	72.1	4.1
p-Iodophenyl	$C_{24}H_{16}IN$	202	64.7	3.6	64.4	3.8
p-Methoxyphenyl	$C_{25}H_{19}NO$	236	85.9	5.4	85.9	5.6
p-Nitrophenyl	$C_{24}H_{16}N_2O_2$	293	79.1	4.4	79.0	4.6
2-Naphthyl	$C_{28}H_{19}N$	206	91.0	5.1	90.8	5.2
2-Thienyl	$C_{22}H_{15}NS$	196	81.2	4.6	81.0	4.6

5-bromo-2-acetothienone the normal chalkones were obtained, whereas with 5-chloro-2-acetothienone the reaction-product was 9-anthrylidene-*bis*-(5-chloro-2-acetothienone) (XXII).



XXII

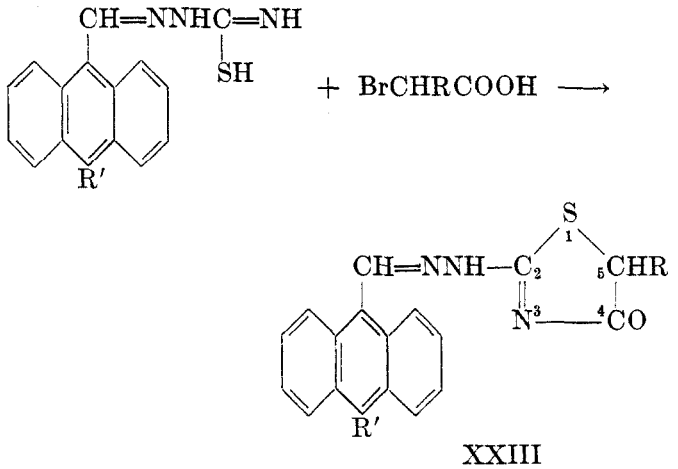
The widespread antitubercular properties encountered in the series of thiosemicarbazones of aldehydes and ketones (10) prompted the preparation of the thiosemicarbazones of 9-anthraldehyde and of 9-methyl-10-anthraldehyde. These were found by Dr. Welsch to inhibit completely the growth of tubercle bacilli (B.C.G. strain) at a concentration of 10^{-6}. An interesting reaction displayed

TABLE III

9-ANTHRALDEHYDE AND 9-METHYL-10-ANTHRALDEHYDE 4-KETO-2-THIAZOLINYL-HYDRAZONES (XXIII)

RADICALS R AND R′	FORMULA	M.P., °C.	ANALYSES			
			Calc'd		Found	
			C	H	C	H
R = R′ = H	$C_{18}H_{13}N_3OS$	355	67.7	4.1	67.5	4.1
R = C_2H_5, R′ = H	$C_{20}H_{17}N_3OS$	278	69.2	4.9	68.7	5.0
R = n-C_4H_9, R′ = H	$C_{22}H_{21}N_3OS$	256	70.4	5.6	70.2	5.4
R = n-$C_{14}H_{29}$, R′ = H	$C_{32}H_{41}N_3OS$	208	74.6	8.0	74.3	8.2
R = n-$C_{16}H_{33}$, R′ = H	$C_{34}H_{45}N_3OS$	200	75.1	8.3	74.8	8.2
R = H, R′ = CH_3	$C_{19}H_{15}N_3OS$	355–357	68.5	4.5	68.2	4.6
R = C_2H_5, R′ = CH_3	$C_{21}H_{19}N_3OS$	287	69.8	5.3	69.6	5.1
R = n-C_4H_9, R′ = CH_3	$C_{23}H_{23}N_3OS$	271	70.9	5.9	70.6	5.8
R = n-$C_{14}H_{29}$, R′ = H_3	$C_{33}H_{43}N_3OS$	178	74.8	8.1	74.5	8.2
R = n-$C_{16}H_{33}$, R′ = CCH_3	$C_{35}H_{47}N_3OS$	172	75.4	8.4	75.1	8.5

by these semicarbazones is their condensation and cyclization with α-halogenated fatty acids to the corresponding 4-keto-2-thiazolinylhydrazones of the general formula XXIII (11), and these are listed in Table III.



XXIII

EXPERIMENTAL

9-Anthraldehyde thiosemicarbazone. 9-Anthraldehyde was prepared according to *Organic Syntheses* (12) in 85% yield; it gave an orange-red coloration with sulfuric acid. The thiosemicarbazone, obtained from this aldehyde and thiosemicarbazide in ethanol solution, crystallized from acetic acid or ethanol in fine yellow needles, which reddened and softened above 210°, and melted at 217°. Like many semicarbazones, this compound did not give satisfactory carbon values in analyses, unless an excess of oxidizing agent was used.

Anal. Calc'd for $C_{16}H_{13}N_3S$: C, 68.8; H, 4.6.

Found: C, 68.4; H, 4.6.

9-Methyl-10-anthraldehyde (II). The reduction of 100 g. of the above aldehyde with 85% hydrazine hydrate (150 g.) and potassium hydroxide (120 g.) in diethylene glycol (350 ml.) yielded 91 g. (97.7%) of 9-methylanthracene, b.p. 198–202°/13 mm. To a mixture of 90 g. of this hydrocarbon with 127 g. of redistilled N-methylformanilide and 90 ml. of *o*-dichloro-

benzene, 130 g. of phosphorus oxychloride was cautiously added. The reaction started at room temperature and continued for 15 minutes. The reaction mixture was subsequently heated for 1½ hours on a water-bath and poured after cooling into 200 g. of sodium acetate in 1000 ml. of water. The solvent was removed by steam-distillation, and the semi-solid brown-red precipitate formed after cooling was triturated with 6 *N* hydrochloric acid, washed with water, and then with a dilute solution of acetic acid. The solid crystallized from acetic acid or ethanol in shiny orange needles, m.p. 173°; yield, 62 g.

Anal. Calc'd for $C_{16}H_{12}O$: C, 86.5; H, 5.5.

Found: C, 86.4; H, 5.4.

The corresponding *semicarbazone* formed fine orange-yellow needles melting above 350° from ethanol. The *thiosemicarbazone* crystallized from acetic acid in fine orange-yellow needles which reddened and softened above 218°, and melted at 230°.

Anal. Calc'd for $C_{17}H_{15}N_3S$: C, 69.6; H, 5.1.

Found: C, 69.4; H, 5.3.

9,10-Dimethylanthracene (I). A mixture of 30 g. of aldehyde II, 50 g. of 85% hydrazine hydrate, 50 g. of potassium hydroxide, and 250 ml. of diethylene glycol was gradually heated with removal of water up to 200°, then refluxed until the thick orange-red froth formed at the beginning had disappeared. After cooling, the reaction mixture was diluted with water and extracted with chloroform. The chloroform was dried over sodium sulfate, the solvent removed, and the residue recrystallized from benzene; large shiny yellow leaflets, m.p. 188° [literature m.p. 183.5–184.5° (15)], yield, over 90%.

9-Styrylanthracenes (IV). To benzylmagnesium chloride made from 20 g. of benzyl chloride and 3.8 g. of magnesium shavings in anhydrous ether (150 ml.), 32 g. of 9-anthraldehyde was added in small portions. The reaction mixture was refluxed for half an hour, and after cooling, was treated with cold dilute sulfuric acid. Benzene was added, and the organic layer was washed with water and dried over sodium sulfate. After removal of the solvent, the solid residue was vacuum-distilled; the portion boiling at 280°/13 mm. crystallized from a mixture of ethanol and benzene in large, sublimable, pale yellow leaflets (7g.) m.p. 226°, giving an orange-red coloration with sulfuric acid.

Anal. Calc'd for $C_{22}H_{16}$: C, 94.3; H, 5.7.

Found: C, 93.9; H, 5.6.

The portion boiling at 280–300°/13 mm. (yield, 21 g.) crystallized from ethanol in shiny pale yellow leaflets, m.p. 132°, giving with sulfuric acid a coloration similar to the above isomer.

Anal. Calc'd for $C_{22}H_{16}$: C, 94.3; H, 5.7.

Found: C, 94.0; H, 5.8.

9-Methyl-10-styrylanthracene (V). 9-Methyl-10-anthraldehyde (4.5 g.) was added to benzylmagnesium chloride made from 5.5 g. of benzyl chloride and 1 g. of magnesium shavings in anhydrous ether. After the usual treatment, 4.5 g. of the expected hydrocarbon, boiling at 300–310°/13 mm. was obtained. This compound crystallized from ethanol in long orange needles, m.p. 157°, giving with sulfuric acid a pink coloration.

Anal. Calc'd for $C_{23}H_{18}$: C, 93.9; H, 6.1.

Found: C, 93.6; H, 6.1.

α-(9-Anthryl)-β-(2-pyridyl)ethylene (VI). A mixture of 3 g. of 9-anthraldehyde, 4 g. of α-picoline, and 10 g. of acetic anhydride was refluxed for 48 hours. After cooling, dilute hydrochloric acid was added, the precipitate was collected and was treated with hot 20% sodium hydroxide. The solid residue obtained crystallized from ethanol in shiny, greenish-yellow needles, m.p. 215°, easily sublimable above 180°, giving with sulfuric acid an orange-red coloration; yield, 2 g.

Anal. Calc'd for $C_{21}H_{15}N$: C, 89.7; H, 5.3.

Found: C, 89.6; H, 5.5.

α-(9-Anthryl)-β-(4-methyl-2-pyridyl)ethylene (VII) was obtained in the same way from 3 g. of 9-anthraldehyde, 4.5 g. of 2,4-lutidine, and 10 g. of acetic anhydride. It crystallized from ethanol in shiny, greenish-yellow needles, m.p. 222°, sublimable above 175°, giving with sulfuric acid an orange coloration; yield, 2 g.

Anal. Calc'd for $C_{22}H_{17}N$: C, 89.4; H, 5.7.
Found: C, 89.2; H, 5.7.

Preparation of intermediates for the synthesis of α-aryl-β-(9-anthryl)acrylonitriles. α- and β-Naphthylacetonitrile were prepared as usual from potassium cyanide and α-chloromethyl- and β-bromomethyl-naphthalene in acetone; the latter compound was obtained from β-methylnaphthalene and N-bromosuccinimide. *p*-Fluoro-, *p*-chloro-, *p*-bromo-, and *p*-iodophenylacetonitrile were similarly prepared from the corresponding *p*-substituted benzyl chlorides. *p*-Fluorobenzyl chloride was obtained from *p*-fluorotoluene by chlorination with sulfuryl chloride in the presence of benzoyl peroxide (13); the three other halogenated benzyl chlorides were prepared by chloromethylation of chloro-, bromo-, and iodo-benzene respectively. As an example, *p*-Iodobenzyl chloride was made in the following way: hydrogen chloride was bubbled into a well-stirred mixture of 244 g. of iodobenzene, 65 g. of paraformaldehyde, 33 g. of 35% aqueous formaldehyde, and 145 g. of zinc chloride, heated on a water-bath for five hours. After cooling, the lower layer was separated, washed with water, then with very dilute sodium hydroxide, and again with water, dried over sodium sulfate, and vacuum-fractionated. Yield, 100 g. of the chloromethyl compound, boiling at 136–140°/15 mm. A mixture of 92 g. of this product, 31 g. of potassium cyanide dissolved in the minimum of water, and 500 ml. of acetone was refluxed for 12 hours. After the usual treatment, 65 g. of *p*-iodophenylacetonitrile, b.p. 172°/13 mm. was obtained. A small amount of the liquid *ortho*-isomer was removed by cooling the crude product and filtering.

2,5-Dimethyl-3-thienylacetonitrile. This new compound was prepared by refluxing for 12 hours a solution of 23 g. of 2,5-dimethyl-3-chloromethylthiophene (14), 12 g. of potassium cyanide (dissolved in a little water), and 200 ml. of acetone. The solvent was distilled off and the reaction product taken up in ether; the ether solution was dried over sodium sulfate, the solvent removed, and the oily residue vacuum-fractionated. Yield, 16 g. of an almost colorless, fluid oil, b.p. 180–185°/15 mm., with an odor of bitter almonds.

Anal. Calc'd for C_8H_9NS: C, 63.5; H, 5.9.
Found: C, 63.2; H, 6.0.

Condensation of anthracene aldehydes with arylacetonitriles. The condensation was performed by shaking the aldehyde and arylacetonitrile in warm ethanol with a few drops of 30% aqueous potassium hydroxide. An almost immediate separation of a solid precipitate was generally observed; the substance was washed with water and recrystallized from a mixture of ethanol and benzene. In the case of *p*-nitrophenylacetonitrile, the alkaline catalyst used was piperidine, and the reaction products were recrystallized from toluene. All the acrylonitriles thus obtained formed yellow to orange sublimable needles, the color of each derivative of 9-methyl-10-anthraldehyde being generally deeper than that of the corresponding derivative of 9-anthraldehyde. All the acrylonitriles gave intense green or brownish-green halochromic colorations with sulfuric acid, except compound XVI and α-(2-naphthyl)-β-(9-methyl-10-anthryl)acrylonitrile, which gave a deep red and a violet color respectively.

9-Anthrylideneacetophenone (XXI; Ar=C_6H_5). A mixture of equimolecular quantities of 9-anthraldehyde and acetophenone in ethanol was shaken with a few drops of 20% aqueous sodium hydroxide. The solid thus obtained was washed with water and recrystallized from a mixture of ethanol and benzene to give fine orange-yellow prisms, m.p. 120°, giving with sulfuric acid a deep green coloration; yield, 85%.

Anal. Calc'd for $C_{23}H_{16}O$: C, 89.6; H, 5.2.
Found: C, 89.9; H, 5.4.

9-Anthrylidene-p-chloroacetophenone (XXI; Ar = C_6H_4Cl) was obtained from *p*-chloroacetophenone and 9-anthraldehyde; it formed from toluene yellow leaflets, m.p. 132°, giving a gree coloration with sulfuric acid.

Anal. Calc'd for $C_{23}H_{15}ClO$: C, 80.5; H, 4.4.
Found: C, 80.3; H, 4.6.

9-Anthrylidene-p-iodoacetophenone (XXI; Ar = C_6H_4I) crystallized from toluene as fine orange needles, m.p. 168°, giving with sulfuric acid a blue coloration.

Anal. Calc'd for $C_{23}H_{15}IO$: C, 63.6; H, 3.5.
Found: C, 63.3; H, 3.6.

9-Anthrylidene-2-acetothienone (XXI; Ar = C_4H_3S) crystallized from ethanol and benzene as long, shiny orange-yellow prisms, m.p. 162°; dark green coloration with sulfuric acid.

Anal. Calc'd for $C_{21}H_{14}OS$: C, 80.2; H, 4.4.

Found: C, 79.9; H, 4.2.

9-Anthrylidene-(5-bromo-2-acetothienone) (XXI; Ar = C_4H_2BrS) formed fine orange-yellow prisms, m.p. 139°; dark green coloration with sulfuric acid.

Anal. Calc'd for $C_{21}H_{13}BrOS$: C, 64.1; H, 3.3.

Found: C, 64.0; H, 3.5.

9-Anthrylidene-bis-(5-chloro-2-acetothienone) (XXII) crystallized from ethanol in fine pale yellow prisms, m.p. 146°, giving with sulfuric acid a pale greenish-yellow coloration.

Anal. Calc'd for $C_{27}H_{18}Cl_2O_2S_2$: C, 64.0; H, 3.5.

Found: C, 63.7; H, 3.6.

Preparation of 4-keto-2-thiazolinylhydrazones of 9-anthraldehyde and 9-methyl-10-anthraldehyde. A suspension of the thiosemicarbazone of the corresponding aldehyde with chloroacetic, α-bromo-*n*-butyric, α-bromocaproic, α-bromopalmitic, or α-bromostearic acid in acetic acid or ethanol was refluxed for five hours in the presence of sodium acetate; after cooling, the precipitate was recrystallized from acetic acid or toluene. Like the thiosemicarbazones themselves, these cyclization products were yellow (in the case of derivatives of 9-anthraldehyde) or orange-yellow (in the case of derivatives of 9-methyl-10-anthraldehyde), and were very difficult to analyze by combustion.

SUMMARY

1. A convenient synthesis for the carcinogenic 9,10-dimethylanthracene is described.

2. Several ethylenic hydrocarbons, nitriles, and ketones derived from anthracene have been prepared for cancer research.

3. A number of thiosemicarbazones and 4-keto-2-thiazolinylhydrazones of the anthracene series have been synthesized for the study of their tuberculostatic properties.

PARIS V^e^, FRANCE

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