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

CARCINOGENIC DERIVATIVES OF CARBAZOLE. II. ISOSTERIC COMPOUNDS OF CARBAZOLE CONTAINING A THIOPHENE NUCLEUS[1]

NG. PH. BUU-HOÏ, NG. HOAN, NG. H. KHÔI, AND NG. D. XUONG

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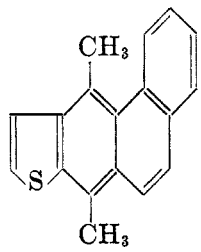
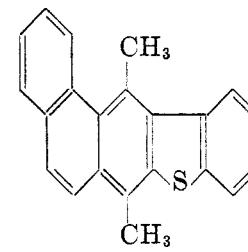
In recent years, a trend of research in chemical carcinogenesis which has proved fruitful has been the preparation and biological study of compounds derved from the basic carcinogenic hydrocarbons by replacement of a benzene nucleus with a heterocyclic one, mostly those of the pyridine and thiophene series.

In 1939, Sempronj and Morelli (1) reported the activity of β-anthraquinoline (an isolog of 1,2-benzanthracene) in the production of carcinoma of the kidney, and Joseph (2) found both 3,4-benzo-8-azaphenanthrene and pyrenoline (an isolog of the potent 3,4-benzopyrene) to be inactive. Fieser and Hershberg (3) synthesized 20-methyl-4-azacholanthrene, an isolog of the important 20-methylcholanthrene, along with other similar compounds. In 1946, Lacassagne, Buu-Hoï, Lecocq, and Rudali (4) discovered a large number of powerful carcinogens among *meso*-substituted benzacridines. In the category of substances bearing a thiophene nucleus, compounds endowed with a high degree of carcinogenicity have also been found. This was the case for 4,9-dimethyl-5,6-benzothiophanthrene (I)



I



II

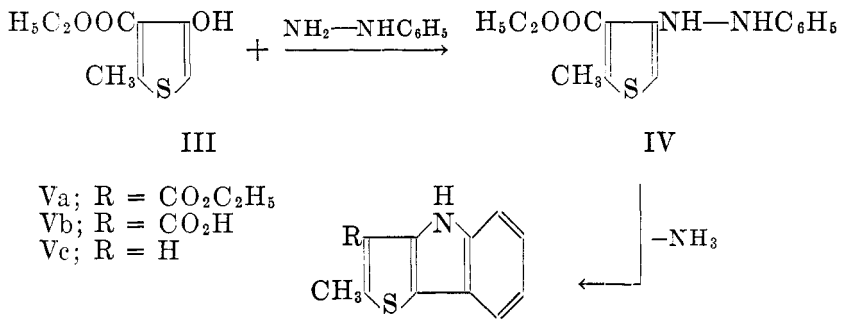
described by Fieser and Sandin (5), and of 4,9-dimethyl-2,3,5,6-dibenzothiophanthrene (II) prepared by Tilak (6). 2-Methyl-5,6-benzothiophanthrene and 2-methyl-7,8-benzothiophanthrene recently synthesized by Buu-Hoï and Hoan (7) are still under biological examination by Professor A. Lacassagne.

In this paper, we report the preparation of a number of isosteric compounds of carbazole, angular benzocarbazoles, and bisangular dibenzocarbazoles which contain a thiophene nucleus in the place of a benzene one. Two lines of synthesis have simultaneously been pursued:

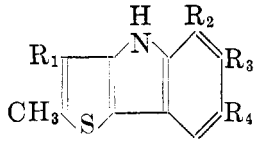
(a) According to Benary and Baravian (8), 3-hydroxy-4-carbethoxy-5-methylthiophene (III), readily obtainable from ethyl acetoacetate by means of a three-step synthesis, reacts with phenylhydrazine in acetic acid medium in such a

[1] The work described in this paper was carried out with the financial support of the U. S. Public Health Service, Federal Security Agency.

way that the transient 3-phenylhydrazido-4-carbethoxy-5-methylthiophene (IV) formed undergoes immediately a Fischer indole ring-closure into 3′,2′:2,3-(4′-carbethoxy-5′-methylthiopheno)indole (Va); the alkaline saponification of the



latter gives 3′,2′: 2,3-(4′-carboxy-5′-methylthiopheno)indole (Vb), which can be readily decarboxylated into 3′,2′:2,3-(5′-methylthiopheno)indole (Vc). We found that the same sequence of reactions could be performed with a series of diversely substituted arylhydrazines, of which the following were successfully employed: *o*-, *m*-, and *p*-tolylhydrazine, *vic.*-*o*-xylylhydrazine, *p*-chloro- and *p*-bromophenylhydrazine, and *p*-xenylhydrazine. The different compounds thus obtained are listed below:



VIa; $R_1 = CO_2C_2H_5$, $R_2 = CH_3$, $R_3 = R_4 = H$
VIb; $R_1 = CO_2H$, $R_2 = CH_3$, $R_3 = R_4 = H$
VIc; $R_1 = R_3 = R_4 = H$, $R_2 = CH_3$.

VIIa; $R_1 = CO_2C_2H_5$, $R_2 = R_4 = H$, $R_3 = CH_3$
VIIb; $R_1 = CO_2H$, $R_2 = R_4 = H$, $R_3 = CH_3$
VIIc; $R_1 = R_2 = R_4 = H$, $R_3 = CH_3$.

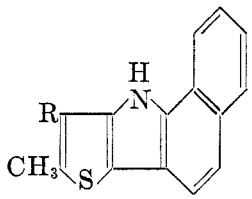
VIIIa; $R_1 = CO_2C_2H_5$, $R_2 = R_3 = H$, $R_4 = CH_3$
VIIIb; $R_1 = CO_2H$, $R_2 = R_3 = H$, $R_4 = CH_3$
VIIIc; $R_1 = R_2 = R_3 = H$, $R_4 = CH_3$

IXa; $R_1 = CO_2C_2H_5$, $R_2 = R_3 = CH_3$, $R_4 = H$
IXb; $R_1 = CO_2H$, $R_2 = R_3 = CH_3$, $R_4 = H$
IXc; $R_1 = R_4 = H$, $R_2 = R_3 = CH_3$.

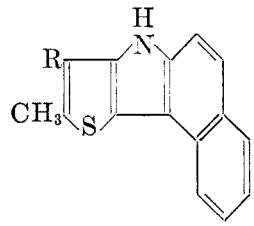
Xa; $R_1 = CO_2C_2H_5$, $R_2 = R_3 = H$, $R_4 = Cl$
Xb; $R_1 = CO_2H$, $R_2 = R_3 = H$, $R_4 = Cl$
Xc; $R_1 = R_2 = R_3 = H$, $R_4 = Cl$.

XIa; $R_1 = CO_2C_2H_5$, $R_2 = R_3 = H$, $R_4 = Br$.

XIIa; $R_1 = CO_2C_2H_5$, $R_2 = R_3 = H$, $R_4 = C_6H_5$.
XIIb; $R_1 = CO_2H$, $R_2 = R_3 = H$, $R_4 = C_6H_5$
XIIc; $R_1 = R_2 = R_3 = H$, $R_4 = C_6H_5$



XIIIa; R = $CO_2C_2H_5$
XIIIb; R = CO_2H
XIIIc; R = H.

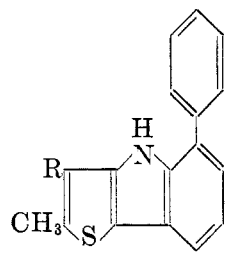


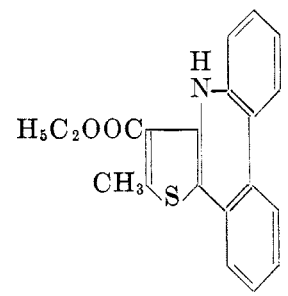
XIVa; R = $CO_2C_2H_5$
XIVb; R = CO_2H
XIVc; R = H

5-Bromo-3′,2′:2,3-(4′-carboxy-5′ -methylthiopheno)indole (XIa) was also obtained by direct treatment of (Va) with the calculated amount of bromine.

By means of α- and β-naphthylhydrazine, the synthesis of 3′,2′:2,3-(5′-methylthiopheno)-6,7-benzoindole (XIII)c and of the isomeric 3′,2′:2,3-(5′-methylthiopheno)-4,5-benzoindole (XIVc) was similarly achieved. The two latter compounds are isosteres of 6-methyl-1,2-benzocarbazole and of 6-methyl-3,4-benzocarbazole respectively, which are now under biological testing for potential carcinogenic properties. Special mention should be made of *o*-xyenylhydrazine, which gave with 3-hydroxy-4-carbethoxy-5-methylthiophene, an indole to which either formula (XVa) or (XVI) could be assigned. In view of the outstanding ease of formation of nitrogen-containing five-membered rings, we give preference to the formula (XVa) over the heptagonal one, which involves cyclisation on both phenyl nuclei.

XVa; R = $CO_2C_2H_5$
XVb; R = CO_2H
XVc; R = H



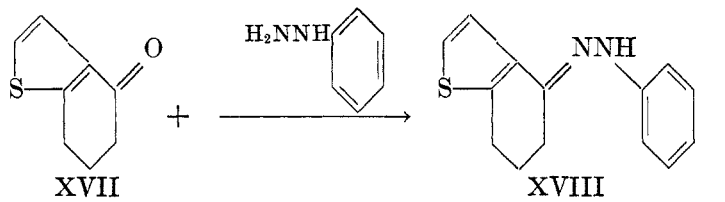


XVI

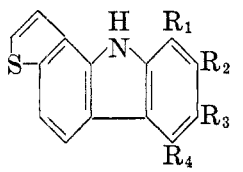
All the substances mentioned above are well-crystallised solids, giving deep halochromic coloration with sulfuric acid and dark colored picrates, as in the carbazole series. 3′,2′:2,3-(5′-Methylthiopheno)indole gave with ethylmagnesium bromide an organometallic compound, which yielded on treatment with dimethyl or diethyl sulfate oily substances believed to be 1-methyl- and 1-ethyl-3′,2′:2,3-(5′-methylthiopheno)indole respectively.

(b) A route towards thiophenocarbazoles which we have devised is the Fischer-Borsche indole ring-closure of various 4-keto-4,5,6,7-tetrahydrothianaphthene arylhydrazones, followed by dehydrogenation of the dihydro intermediates obtained. Thus, 4-keto-4,5,6,7-tetrahydrothianaphthene phenylhydrazone (XVIII) was converted by means of a solution of dry hydrogen chloride in pure

acetic acid into 3,4-dihydro-3′,2′:1,2-thiophenocarbazole (XIX) and this readily gave 3′,2′:1,2-thiophenocarbazole (XX) by heating with chloranil, a reagent previously used with success by Barclay and Campbell (9) for the dehydrogenation of tetrahydrocarbazoles, and more recently by Buu-Hoï, Hoan, and Khôi (10) for the synthesis of various dibenzocarbazoles.

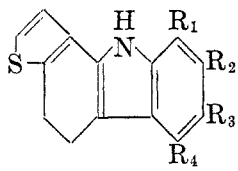


The replacing of phenylhydrazine in the above synthesis by *o*-, *m*-, and *p*-tolylhydrazine, *vic.-o*- and *p*-xylylhydrazine, and *p*-xenylhydrazine, gave rise to 8-methyl- (XXIa), 7-methyl- (XXIIa), 6-methyl- (XXIIIa), 7,8-dimethyl- (XXIVa), 5,8-dimethyl- (XXV), and 6-phenyl-3′,2′:1,2-thiophenocarbazole (XXVIa). In the course of these syntheses, the following dihydro compounds



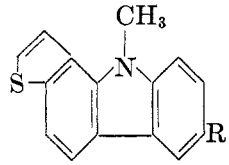
XXI a; $R_1 = CH_3$, $R_2 = R_3 = R_4 = H$
XXII a; $R_1 = R_3 = R_4 = H$, $R_2 = CH_3$
XXIIIa; $R_1 = R_2 = R_4 = H$, $R_3 = CH_3$
XXIVa; $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$.
XXV ; $R_1 = R_4 = CH_3$, $R_2 = R_3 = H$.
XXVIa; $R_1 = R_2 = R_4 = H$, $R_3 = C_6H_5$.

were isolated: 8-methyl- (XXIb), 7-methyl- (XXIIb), 6-methyl- (XXIIIb), 7,8-dimethyl- (XXIVb), and 6-phenyl-3,4-dihydro-3′,2′-1,2-thiophenocarbazole (XXVIb).



XXI b; $R_1 = CH_3$, $R_2 = R_3 = R_4 = H$
XXII b; $R_1 = R_3 = R_4 = H$, $R_2 = CH_3$
XXIIIb; $R_1 = R_2 = R_4 = H$, $R_3 = CH_3$
XXIVb; $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$
XXVIb; $R_1 = R_2 = R_4 = H$, $R_3 = C_6H_5$.

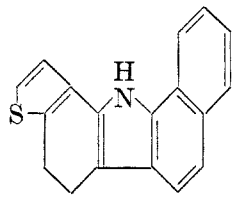
In view of the slight activity by Lacassagne, Buu-Hoï, and Zajdela (11) for 9-methyl-1,2-benzocarbazole, and of the generally enhancing influences of *meso*-substitution upon carcinogenicity (*viz.*, the cases of 9,10-dimethyl-1,2-



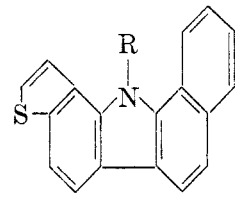
XXVII ; R = H
XXVIII; R = CH_3.

benzanthracene and of the carcinogenic benzacridines), we prepared 9-methyl- (XXVII) and 6,9-dimethyl-3′2′:1,2-thiophenocarbazole (XXVIII) by treatment with dimethyl sulphate of 3′,2′:1,2-thiophenocarbazylmagnesium bromide and 6-methyl-3′,2′:1,2-thiophenocarbazylmagnesium bromide respectively.

The Fischer-Borsche indole synthesis, applied to 4-keto-4,5,6,7-tetrahydrothianaphthene and α-naphthylhydrazine, yielded 3,4-dihydro-3′,2′:1,2-thiopheno-7,8-benzocarbazole (XXIX), which was dehydrogenated by chloranil to 3′,2′:1,2-thiopheno-7,8-benzocarbazole (XXXa); successive treatment of the latter with ethylmagnesium bromide and dimethyl sulfate yielded the correspond-

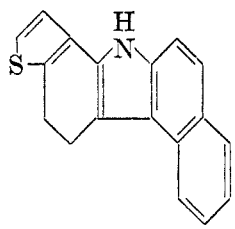


XXIX

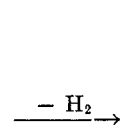


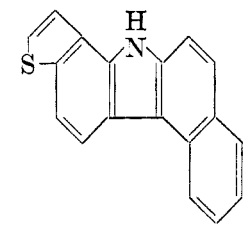
XXXa; R = H
XXXb; R = CH_3

ing N-methyl derivative (XXXb). The same sequence of reactions performed with β-naphthylhydrazine, resulted in 3′,2′:1,2-thiopheno-5,6-benzocarbazole (XXXII) through the dihydro-compound (XXXI).



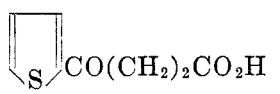
XXXI



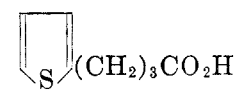


XXXII

It should be mentioned that the 4-keto-4,5,6,7-tetrahydrothianaphthene used throughout this research was prepared by cyclization of γ-2-thienylbutyryl chloride according to the excellent procedure of Fieser and Kennelly (12). These authors prepared γ-2-thienylbutyric acid (XXXIV) by means of the Clemmensen reduction of β-2-thenoylpropionic acid (XXXIII) at low temperature; we have found now that a much more convenient method for the preparation of (XXXIV)



XXXIII



XXXIV

is the application to the ketoacid (XXXIII) of Huang-Minlon's modification of the Wolff-Kishner reaction (13), using hydrazine hydrate and diethylene glycol.

The various new compounds mentioned above are under biological testing by Professor Lacassagne. It may be recalled that the isosteres of (XXXa) and (XXXII), 1,2,7,8- and 1,2,5,6-dibenzocarbazole, are carcinogenic substances

with interesting peculiarities in their action, as for instance the production of remote tumors in the liver (14).

Acknowledgment. Our thanks are due to Miss P. F. Boshell, M. A. (Oxon.) for helpful assistance in this work.

EXPERIMENTAL[2]

Preparation of intermediates. The various *arylhydrazines* used in these experiments were prepared in the form of their hydrochlorides by reduction of the appropriate aryldiazonium chlorides with stannous chloride.

3-Hydroxy-4-carbethoxy-5-methylthiopthene (III). The Benary-Baravian procedure for the preparation of this compound (8) was followed except in the first step, the synthesis of ethyl β-aminocrotonate being carried out as follows: a stream of dry ammonia was bubbled for three hours into a solution of 130 g. of ethyl acetoacetate in 150 ml. of anhydrous benzene, cooled to around 4°. The half-solid mixture was kept overnight and about 100 ml. of liquid ammonia was stirred into it. After the usual treatment, over 110 g. of ethyl β-aminocrotonate was obtained.

γ-2-Thienylbutyric acid (XXXIV). β-2-Thenoylpropionic acid (40 g.) [prepared from thiophene, succinic anhydride, and aluminum chloride, according to Fieser and Kennelly (12)] was added cautiously to a solution of 40 g. of potassium hydroxide in 30 ml. of 50% hydrazine hydrate and 250 ml. of diethylene glycol. The mixture was boiled for one hour and a half for water removal, the temperature rising progressively up to 195°. The refluxing was then continued for five more hours, and the diethylene glycol distilled off under low pressure. The residue was dissolved in water, and the clear solution obtained was acidified with hydrochloric acid. The oily precipitate was taken up in ether, the ether solution dried over calcium chloride and filtered. After removal of the solvent, the residue was vacuum-distilled. γ-2-Thienylbutyric acid, b.p. 170–172°/14 mm. was thus obtained rapidly (yield: 25 g.).

7-Methyl-3',2':2,3-(4'-carboethoxy-5'-methylthiopheno)indole (VIa) and derivatives. A mixture of 10 g. of the ester (III), 15.5 g. of *o*-tolylhydrazine hydrochloride, 9 g. of sodium acetate, 75 ml. of acetic acid, and 25 ml. of water was refluxed three hours. After cooling and dilution with water, the precipitate obtained was recrystallized twice from benzene (charcoal), giving fine yellowish needles, m.p. 136°. The low yield obtained (30%) was probably due to the steric hindrance exerted by the *o*-methyl radical.

Anal. Calc'd for $C_{15}H_{15}NO_2S$: N, 5.1. Found: N, 5.2.

7-Methyl-3',2':2,3-(4'-carboxy-5'-methylthiopheno)indole (VIb) was obtained from the foregoing ester by saponification with potassium hydroxide in ethanol. It formed from chlorobenzene a colorless microcrystalline powder, m.p. 262° (decomp.).

Anal. Calc'd for $C_{13}H_{11}NO_2S$: N, 5.9. Found: N, 5.7.

Dry vacuum-distillation of a mixture of equal quantities of the foregoing acid and of calcium hydroxide yielded *7-methyl-3',2':2,3-(5'-methylthiopheno)indole* (VIc), which crystallized from petroleum ether in fine yellowish prisms, m.p. 110°, giving a deep brown-red coloration with pure sulfuric acid.

Anal. Calc'd for $C_{12}H_{11}NS$: N, 6.9. Found: N, 7.0.

The *picrate* thereof crystallized from benzene in fine brown-violet needles, m.p. 152°. The N-alkylation of (VIc) was performed as follows: 0.9 g. of that compound was added to a solution of ethylmagnesium bromide made from 0.24 g. of magnesium and 1.5 g. of ethyl bromide in 20 ml. of anhydrous ether. The compound dissolved with evolution of ethane; the mixture was refluxed for ten minutes, then cooled, and 1.3 g. of dimethyl sulfate was added. After ten minutes of further heating, the mixture was poured into cooled, dilute sulfuric acid, the reaction-product taken up in benzene, the benzene layer washed with an aqueous solution of sodium hydroxide and then with water, the solvent removed,

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

and the residue vacuum-distilled. *1,7-Dimethyl-3',2':2,3-(5'-methylthiopheno)indole* was thus obtained as a yellow viscous oil, b.p. 235–240°/12 mm.

Anal. Calc'd for $C_{13}H_{13}NS$: N, 6.5. Found: N, 6.9.

1-Ethyl-7-methyl-3',2':2,3-(5'-methylthiopheno)indole was similarly obtained by means of diethyl sulfate (1.5 g.) in the form of a yellow oil, b.p. 235–245°/12 mm.

6-Methyl-3',2':2,3-(4'-carbethoxy-5'-methylthiopheno)indole (VIIa) and derivatives. The condensation of (III) (10 g.) with *m*-tolylhydrazine hydrochloride (15.5 g.), performed in the usual way, gave an almost quantitative yield of the *ester* (VIIa), crystallizing from benzene in fine yellowish needles, m.p. 134°.

Anal. Calc'd for $C_{13}H_{11}NO_2S$: N, 5.1. Found: N, 5.0.

6-Methyl-3',2':2,3-(4'-carboxy-5'-methylthiopheno)indole (VIIb) formed fine colorless prisms from acetic acid, m.p. 285° (decomp.).

Anal. Calc'd for $C_{13}H_{11}NO_2S$: N, 5.9. Found: N, 5.6.

6-Methyl-3',2':2,3-(5'-methylthiopheno)indole (VIIc) formed long glinting needles from ethanol, m.p. 188°; the *picrate* crystallized from benzene in silky brown-violet prisms m.p. 173°.

Anal. Calc'd for $C_{12}H_{11}NS$: N, 6.9. Found: N, 6.8.

5-Methyl-3',2':2,3-(4'-carbethoxy-5'-methylthiopheno)indole (VIIIa) and derivatives. The *ester* (yield: 98%) formed microscopic needles, m.p. 170°, from ethanol.

Anal. Calc'd for $C_{15}H_{15}NO_2S$: N, 5.2. Found: N, 5.2.

The *free acid* (VIIIb) crystallized from ethanol in colorless needles, m.p. 302° (decomp.).

Anal. Calc'd for $C_{13}H_{11}NO_2S$: N, 5.8. Found: N, 5.7.

5-Methyl-3',2':2,3-(5'-methylthiopheno)indole (VIIIc) crystallized from ethanol in fine yellowish needles m.p. 156°, giving the usual deep brown-red coloration with sulfuric acid; its *picrate* formed fine brown-violet needles, m.p. 180°.

Anal. Calc'd for $C_{12}H_{11}NS$: N, 6.6. Found: N, 6.8.

6,7-Dimethyl-3',2':2,3-(4'-carbethoxy-5'-methylthiopheno)indole (IXa) and derivatives. A low yield (*circa* 50%) of the *ester* (IXa) was obtained (steric hindrance). Yellowish needles, m.p. 142° from chlorobenzene.

Anal. Calc'd for $C_{16}H_{17}NO_2S$: N, 4.9. Found: N, 5.1.

The *free acid* (IXb) crystallized from benzene in tiny colorless needles, m.p. 250°.

Anal. Calc'd for $C_{14}H_{13}NO_2S$: N, 5.3. Found: N, 5.4.

6,7-Dimethyl-3',2':2,3-(5'-methylthiopheno)indole (IXc) formed fine brilliant yellowish needles, m.p. 165° from benzene; its *picrate* formed silky brown-violet needles, m.p. 145°.

Anal. Calc'd for $C_{13}H_{13}NS$: N, 6.5. Found: N, 6.6.

5-Chloro-3',2':2,3-(4'-carbethoxy-5'-methylthiopheno)indole (Xa) and derivatives. The condensation of (III) (3.7 g.) with *p*-chlorophenylhydrazine hydrochloride (5.5 g.), performed in the usual way, gave an almost quantitative yield of the *ester* (Xa); this formed silky colorless leaflets, m.p. 208° from chlorobenzene.

Anal. Calc'd for $C_{14}H_{12}ClNO_2S$: N, 4.8 Found: N, 5.0.

The *free acid* (Xb) crystallized from chlorobenzene in fine colorless prisms, m.p. 325° (decomp.).

Anal. Calc'd for $C_{12}H_8ClNO_2S$: N, 5.2. Found: N, 5.0.

5-Chloro-3',2':2,3-(5'-methylthiopheno)indole (Xc) was obtained by vacuum-heating the foregoing acid alone; it crystallized from ethanol in fine colorless needles m.p. 162°, giving the usual coloration with pure sulfuric acid. The corresponding *picrate* formed brown-red silky needles, m.p. 152° from benzene.

Anal. Calc'd for $C_{11}H_8ClNS$: N, 6.3. Found: N, 6.4.

5-Bromo-3',2':2,3-(4'-carbethoxy-5'-methylthiopheno)indole (XIa). (a) An ice-cooled solution of 1.28 g. of the ester (Va) in 20 ml. of acetic acid was treated with 0.8 g. of bromine dissolved in 10 ml. of acetic acid; after ten minutes, the mixture was poured on to ice, the precipitate collected, and recrystallized from ethanol. Fine colorless silky needles, m.p. 215° were thus obtained (yield 1.5 g).

(b) An almost quantitative yield of the same substance was obtained in the condensa-

tion of (III) (3 g.) with *p*-bromophenylhydrazine hydrochloride (5.5 g.) following the usual procedure. The bromination of (Va) by means of N-bromosuccinimide did not lead to the same product. This point is being further investigated.

Anal. Calc'd for $C_{14}H_{12}BrNO_2S$: N, 4.1. Found: N, 4.2.

5-Phenyl-3',2':2,3-(4'-carbethoxy-5'-methylthiopheno)indole (XIIa) and derivatives. The condensation of (III) (10 g.) with *p*-xenylhydrazine hydrochloride (15 g.) and sodium acetate (9 g.) in 75% acetic acid (100 ml.) gave a quantitative yield of (XIIa); this crystallized from acetic acid or chlorobenzene in silky colorless needles, m.p. 172°.

Anal. Calc'd for $C_{20}H_{17}NO_2S$: N, 4.2. Found: N, 4.2.

The *free acid* (XIIb) formed a colorless microcrystalline powder, m.p. 266° from chlorobenzene.

Anal. Calc'd for $C_{18}H_{13}NO_2S$: N, 4.5. Found: N, 4.2.

5-Phenyl-3',2':2,3-(5'-methylthiopheno)indole (XIIc) formed colorless needles, m.p. 160° from ligroin or ethanol, giving a greenish-brown coloration with sulfuric acid.

Anal. Calc'd for $C_{17}H_{13}NS$: N, 5.3. Found: N, 5.4.

Condensation of (III) with o-hydrazinodiphenyl. The ester (III) (10 g.) was heated with *o*-hydrazinodiphenyl hydrochloride (15 g.) in 75% acetic acid (100 ml.) in the presence of sodium acetate (9 g.).

7-Phenyl-3',2':2,3-(4'-carbethoxy-5'-methylthiopheno)indole (XVa ?) (15 g.), crystallized from chlorobenzene in colorless glinting needless, m.p. 124°.

Anal. Calc'd for $C_{20}H_{17}NO_2S$: N, 4.2. Found: N, 4.3.

The *free acid* (XVb ?) formed colorless light leaflets, m.p. 310° (decomp.) from chlorobenzene.

Anal. Calc'd for $C_{18}H_{13}NO_2S$: N, 4.5. Found: N, 4.3.

7-Phenyl-3',2':2,3-(5'-methylthiopheno)indole (XVc ?) crystallized from ethanol in fine glinting colorless needles, m.p. 156°, giving with sulfuric acid a bluish coloration which rapidly became brown-red. The *picrate* is red.

Anal. Calc'd for $C_{17}H_{13}NS$: N, 5.3. Found: N, 5.2.

3',2':2,3-(4'-Carbethoxy-5'-methylthiopheno)-6,7-benzoindole (XIIIa) and derivatives. The thiophene (III) (9 g.) condensed with 15 g. of α-naphthylhydrazine hydrochloride in 100 ml. of 75% acetic acid in the presence of 8.5 g. of sodium acetate, gave the *ester* (XIIIa) in 90% yield. Fine colorless needles, m.p. 142°, from methanol.

Anal. Calc'd for $C_{18}H_{15}NO_2S$: N, 4.5. Found: N, 4.5.

The corresponding *acid* formed needles, m.p. 320° from ethanol.

Anal. Calc'd for $C_{16}H_{11}NO_2S$: N, 5.0. Found: N, 5.1.

3',2':2,3-(5'-Methylthiopheno)-6,7-benzoindole (XIIIc) crystallized from chlorobenzene in glinting colorless prisms, m.p. 165°, giving with sulfuric acid a violet coloration which rapidly turned brown-red. The *picrate* formed violet needles, m.p. 184° from benzene.

Anal. Calc'd for $C_{15}H_{11}NS$: N, 5.9. Found: N, 6.0.

3',2':2,3-(4'-Carbethoxy-5'-methylthiopheno)-4,5-benzoindole (XIVa) and derivatives. The condensation of (III) with β-naphthylhydrazine hydrochloride, performed as in the foregoing example, gave an equally good yield of the *ester* (XIVa), crystallizing from benzene in silky colorless needles, m.p. 209°.

Anal. Calc'd for $C_{18}H_{15}NO_2S$: N, 4.5. Found: N, 4.6.

The *free acid* formed fine violet-tinged needles, m.p. 318° from chlorobenzene.

Anal. Calc'd for $C_{16}H_{11}NO_2S$: N, 5.0. Found: N, 4.9.

3',2':2,3-(5'-Methylthiopheno)-4,5-benzoindole (XIVc) formed silky colorless prisms, m.p. 152° from chlorobenzene, giving a deep brown-red coloration with sulfuric acid. The *picrate* crystallized from benzene in fine violet prisms, m.p. 175°.

Anal. Calc'd for $C_{15}H_{11}NS$: N, 5.9. Found: N, 6.2.

3,4-Dihydro-3',2':1,2-thiophenocarbazole (XIX). A solution of 1.5 g. of the ketone (XVII) and 2 g. of phenylhydrazine in 25 ml. of ethanol was refluxed for thirty minutes; the cooled mixture was poured into water, the crude phenylhydrazone (XVIII) washed with water, and vacuum-distilled; it was then refluxed for five minutes with 10 ml. of a saturated solu-

tion of hydrochloric acid in water, the solid obtained collected, washed with water, and recrystallized from benzene. Fine colorless prisms (yield: 1.5 g.), m.p. 183°, giving an orange-yellow coloration with sulfuric acid, and a dark violet molecular compound with *picric acid.*

Anal. Calc'd for $C_{14}H_{11}NS$: N, 6.2. Found: N, 6.3.

3',2':1,2-Thiophenocarbazole (XX). A mixture of the foregoing compound (1 g.), chloranil (1.2 g.), and dry xylene (50 ml.) was heated at 120° for three hours; the solution obtained was washed with dilute aqueous caustic soda, then with water, and dried over calcium chloride. The solvent was removed *in vacuo*, and the solid residue recrystallized twice from benzene; glinting colorless needles, m.p. 237°, giving with *picric acid* a dark violet molecular compound, and with sulfuric acid a yellow coloration which rapidly changed into blue.

Anal. Calc'd for $C_{14}H_9NS$: N, 6.2. Found: N, 6.2.

9-Methyl-3',2':1,2-thiophenocarbazole (XXVII). To a solution in ether of a Grignard reagent made from 0.3 g. of ethyl bromide and 0.1 g. of magnesium was added 0.2 g. of (XX) (evolution of ethane ensued); the mixture was refluxed for thirty minutes, then cooled, and 0.1 g. of dimethyl sulfate added. After further refluxing for thirty minutes, the reaction product was decomposed with cold, dilute sulfuric acid, the solid formed collected, washed with water, and recrystallized from benzene. Fine colorless needles, m.p. 196°, giving with sulfuric acid a yellow coloration which rapidly changed into green. The *picrate* is dark violet.

Anal. Calc'd for $C_{15}H_{11}NS$: N, 5.9. Found: N, 6.1.

8-Methyl-3,4-dihydro-3',2':1,2-thiophenocarbazole (XXIb). The *o*-tolylhydrazone of the ketone (XVII) was prepared by refluxing for an hour a mixture of 1.2 g. of (XVII), 2.4 g. of *o*-tolylhydrazine hydrochloride, and 3 g. of sodium acetate in 30 ml. of ethanol. The indolization was performed in the usual way; (XXIb) crystallized from ligroin in yellowish prisms, m.p. 163°, very soluble in benzene, and giving with sulfuric acid a yellow coloration which turned blue; yield: 0.6 g. The *picrate* is violet.

Anal. Calc'd for $C_{15}H_{13}NS$: N, 5.8. Found: N, 5.8.

8-Methyl-3',2':1,2-thiophenocarbazole (XXIa). Crystallized from benzene in fine almost colorless prisms, m.p. 190°, giving with sulfuric acid the same coloration as above. The *picrate* formed silky, violet needles, m.p. 208°.

Anal. Calc'd for $C_{15}H_{11}NS$: N, 5.9. Found: N, 5.6.

7-Methyl-3,4-dihydro-3',2':1,2-thiophenocarbazole (XXIIb). Formed a colorless, microcrystalline powder, m.p. 159° from ligroin (yield: 0.9 g.). The coloration with sulfuric acid was orange-yellow, turning into blue.

Anal. Calc'd for $C_{15}H_{13}NS$: N, 5.8. Found: N, 5.5.

7-Methyl-3',2':1,2-thiophenocarbazole (XXIIa). Glinting, yellowish needles (from benzene), m.p. 255°, which sublimed easily above 200°.

Anal. Calc'd for $C_{15}H_{11}NS$: N, 5.9. Found: N, 5.8.

6-Methyl-3,4-dihydro-3',2':1,2-thiophenocarbazole (XXIIIb). Crystallized from benzene in colorless needles, m.p. 205°, giving with sulfuric acid an orange coloration which turned green, yield: 1.1 g.

Anal. Calc'd for $C_{15}H_{13}NS$: N, 5.8. Found: N, 5.6.

6-Methyl-3',2':1,2-thiophenocarbazole (XXIIIa). Formed fine glinting yellowish prisms, m.p. 264° from benzene.

Anal. Calc'd for $C_{15}H_{11}NS$: N, 5.9. Found: N, 5.8.

6,9-Dimethyl-3',2':1,2-thiophenocarbazole (XXVIII). The N-alkylation of (XXIIIa) was performed with dimethyl sulfate as in the case of (XXVII). The product crystallized from methanol in colorless needles, m.p. 173°, giving with sulfuric acid an orange coloration turning green.

Anal. Calc'd for $C_{16}H_{13}NS$: N, 5.5. Found: N, 5.4.

7,8-Dimethyl-3,4-dihydro-3',2':1,2-thiophenocarbazole (XXIVb). Yellowish microcrystalline powder (from ligroin), m.p. 160°, giving with sulfuric acid a yellow coloration turning green; yield: 0.8 g. from 1.2 g. of (XVII) and 2 g. of *vic.-o*-xylylhydrazine hydrochloride.

Anal. Calc'd for $C_{16}H_{15}NS$: N, 5.5. Found: N, 5.6.

7,8-Dimethyl-3',2':1,2-thiophenocarbazole (XXIVa). Almost colorless needles (from benzene) m.p. 206°; the *picrate* is deep violet.

Anal. Calc'd for $C_{16}H_{13}NS$: N, 5.5. Found: N, 5.6.

5,8-Dimethyl-3',2':1,2-thiophenocarbazole (XXV). The corresponding dihydro compound could not be isolated in a pure state, owing to its great oxidizability. The compound (XXV) crystallized from ligroin in yellowish needles, m.p. 170°, giving with sulfuric acid a yellow coloration turning green. Yield: 0.8 g. from 1.2 g. of (XVII) and 2 g. of *p*-xylylhydrazine.

Anal. Calc'd for $C_{16}H_{13}NS$: N, 5.5. Found: N, 5.4.

6-Phenyl-3,4-dihydro-3',2':1,2-thiophenocarbazole (XXVIb), formed yellowish needles, m.p. 166° from benzene; gave with sulfuric acid an orange coloration turning green, and with *picrate acid* a violet molecular compound; yield: 1.1 g. from 1.2 g. of (XVII) and 2.7 g. of *p*-xenylhydrazine hydrochloride.

Anal. Calc'd for $C_{20}H_{15}NS$: N, 4.6. Found: N, 4.8.

6-Phenyl-3',2':1,2-thiophenocarbazole (XXVIa). Glinting, colorless leaflets (from benzene), m.p. 244° (abundant sublimation above 240°); the corresponding *picrate* crystallized from benzene in silky, violet needles, m.p. 171°.

Anal. Calc'd for $C_{20}H_{13}NS$: N, 4.6. Found: N, 4.6.

3,4-Dihydro-3',2':1,2-thiopheno-7,8-benzocarbazole (XXIX), crystallized from benzene in fine yellowish prisms, m.p. 225°, giving with sulfuric acid a violet coloration turning into dark green; the corresponding *picrate* is deep violet; yield: 1.5 g. from 1.5 g. of (XVII), 2.8 g. of α-naphthylhydrazine hydrochloride, and 3 g. of sodium acetate.

Anal. Calc'd for $C_{18}H_{13}NS$: N, 5.0. Found: N, 5.2.

3',2':1,2-Thiopheno-7,8-benzocarbazole (XXXa). Glistening yellowish leaflets (from benzene), m.p. 232°, giving with sulfuric acid a deep red coloration, and with *picric acid* a dark violet, molecular compound.

Anal. Calc'd for $C_{18}H_{11}NS$: N, 5.1. Found: N, 5.1.

9-Methyl-3',2':1,2-thiopheno-7,8-benzocarbazole (XXXb), crystallized from methanol in fine yellowish needles, m.p. 251°, giving with sulfuric acid a dark brown-red coloration.

Anal. Calc'd for $C_{19}H_{13}NS$: N, 4.8. Found: N, 4.9.

3,4-Dihydro-3',2':1,2-thiopheno-5,6-benzocarbazole (XXXI), crystallized from benzene in yellowish prisms, m.p. 213–214°, giving a dark brown-red coloration with sulfuric acid; yield: 1.5 g.

Anal. Calc'd for $C_{18}H_{13}NS$: N, 5.0. Found: N, 5.2.

3',2':1,2-Thiopheno-5,6-benzocarbazole (XXXII), formed from benzene yellowish prisms, m.p. 223°, giving with sulfuric acid a brown-red coloration turning into dark green; the *picrate* crystallized from benzene in silky, dark violet needles, m.p. 209°.

Anal. Calc'd for $C_{15}H_{11}NS$: N, 5.1. Found: N, 5.3.

SUMMARY

1. The condensation of 3-hydroxy-4-carbethoxy-5-methylthiophene with a series of arylhydrazines has been investigated with the view of obtaining isosteric compounds of carbazole containing a thiophene nucleus.

2. The Fischer-Borsche synthesis of a number of thiophene analogs of carcinogenic mono- and di-benzocarbazoles from 4-keto-4,5,6,7-tetrahydrothianaphthene and various arylhydrazines is reported.

PARIS V^e^, FRANCE

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