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

POTENTIAL NITROGEN-HETEROCYCLE CARCINOGENS. III. NEW DERIVATIVES OF N-ETHYLCARBAZOLE[1]

NG.PH. BUU-HOÏ AND RENÉ ROYER

Received August 1, 1949

At the present stage of chemical cancer research, it is known that, starting from simple aromatic hydrocarbons inactive by themselves, it is possible to produce carcinogenic compounds in two different ways: firstly, by addition of supplementary aromatic rings or hydrocarbon radicals, and secondly, by introduction of certain functional groups such as $—NH_2$, $—N(CH_3)_2$, $—NHCOCH_3$, $—NO_2$, etc. The first line of research has been extensively investigated over the last two decades, and has resulted in the discovery of the largest number of carcinogens hitherto known (1). Although the second has been of more recent date, the examples so far recorded indicate that it may be no less fruitful a basis for research; thus, amination of naphthalene leads to β-naphthylamine, an agent of cancer of the bladder (2), and to 1,5-naphthylenediamine which produces lympho- and myelo-sarcomas by subcutaneous injection (3). Similarly, β-amination of the harmless tricyclic hydrocarbons fluorene and anthracene transforms them into 2-aminofluorene and 2-anthramine, two carcinogens of strikingly versatile activity (4).

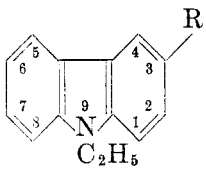
It is known that addition of benzene rings to carbazole or to N-alkylcarbazoles results in carcinogenic substances such as N-methyl-1,2-benzocarbazole (5), 1,2,5,6-, 1,2,7,8-, and 3,4,5,6-dibenzocarbazole (6) or N-ethyl-3,4,5,6-dibenzocarbazole (7). This paper deals with a study of 9-ethylcarbazole carried out mainly along the second line of research outlined above. Of the many compounds thus synthesized for biological investigation by Professor A. Lacassagne, some had already been prepared by other methods, but the rest were hitherto unknown.

3-Acetyl-9-ethylcarbazole (I) (8), best prepared by means of a Friedel-Crafts reaction from 9-ethylcarbazole, acetyl chloride, and aluminum chloride in benzene, was reduced to 3,9-diethylcarbazole (II) with amalgamated zinc and hydrochloric acid. Treatment of (II) with bromine in acetic acid resulted in 6-bromo-3,9-diethylcarbazole (XVI). Clemmensen reduction of 3,6-diacetyl-9-ethylcarbazole (XVII), a by-product in the acetylation of 9-ethylcarbazole (8), yielded 3,6,9-triethylcarbazole (XVIII). A substance isomeric with the latter is 3-isobutyl-9-ethylcarbazole (IV) obtained through similar reduction of 3-isobutyryl-9-ethylcarbazole (III), a liquid ketone prepared from 9-ethylcarbazole and isobutyryl chloride in the usual way.

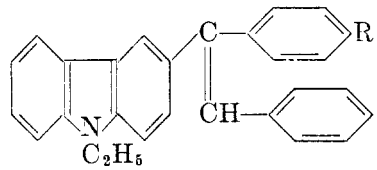
n-Butyroylation of 9-ethylcarbazole yielded a mixture of 3-*n*-butyroyl-9-ethylcarbazole (V) with but little 3,6-di-*n*-butyroyl-9-ethylcarbazole (XIX), and in the case of *n*-octanoylation, no sizable amount of a disubstituted product was

[1] For part II of this series see: Buu-Hoï, *et al.*, *J. Org. Chem.*, **14**, 802 (1949).

obtained, 3-*n*-octanoyl-9-ethylcarbazole (VI) being the sole compound isolated in a pure state. On the other hand, phenacetylation gave less 3-phenacetyl-9-



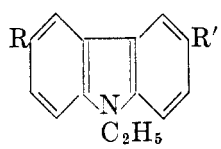
I	R = $COCH_3$	VIII	R = CO–C$_6$H$_4$–OCH_3
II	R = C_2H_5	IX	R = $COCH_2Cl$
III	R = $COCH(CH_3)_2$	X	R = $NHCOCH_3$
IV	R = $CH_2CH(CH_3)_2$	XI	R = $NHCOC_2H_5$
V	R = $CO(CH_2)_2CH_3$	XII	R = COOH
VI	R = $CO(CH_2)_6CH_3$	XIII	R = $CONH_2$
VII	R = $CO(CH_2)C_6H_5$		



XIV R = H
XV R = OCH_3

ethylcarbazole (VII) than 3,6-diphenacetyl-9-ethylcarbazole (XX). This latter substance gave 3,6-di(β-phenylethyl)-9-ethylcarbazole (XXI) on Clemmensen reduction.

Treatment of 3-benzoyl-9-ethylcarbazole (8) with benzylmagnesium chloride resulted in a tertiary carbinol which was dehydrated on vacuum-distillation into α,β-diphenyl-β-(9-ethylcarbazol-3-yl)ethylene (XIV), a substance whose interest lies in its structural connection with both the estrogenic α,β,β-triphenylethylene and the carcinogenic aminostilbenes (9). In the same series, α-phenyl-β-anisyl-β-(9-ethylcarbazol-3-yl)ethylene (XV) was prepared from benzylmagnesium chloride and 3-anisoyl-9-ethylcarbazole (VIII), a ketone which was readily obtained from anisoyl chloride, 9-ethylcarbazole, and aluminum chloride in benzene.

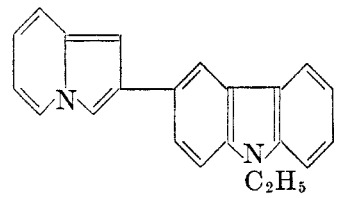


XVI	R = Br, R′ = C_2H_5
XVII	R = R′ = $COCH_3$
XVIII	R = R′ = C_2H_5
XIX	R = R′ = $CO(CH_2)_2CH_3$
XX	R = R′ = $COCH_2C_6H_5$
XXI	R = R′ = $(CH_2)_2C_6H_5$
XXII	R = Br, R′ = COOH
XXIII	R = R′ = COOH

The oxidation of 3-acetyl-9-ethylcarbazole by means of sodium hypobromite in the presence of dioxane gave a fairly good yield of 9-ethylcarbazole-3-carboxylic acid (XII), a compound which had previously been obtained with less ease by Gilman and Kirby (12) through carbonation of the lithio derivative of 9-ethylcarbazole. This acid gave on treatment with thionyl chloride a solid *chloride* which was transformed into 9-ethylcarbazole-3-carboxamide (XIII) by aqueous ammonia; with bromine in acetic acid it gave 6-bromo-9-ethylcarbazole-3-carboxylic acid (XXII). 9-Ethylcarbazole-3,6-dicarboxylic acid (XXIII) was similarly obtained in high yield by hypobromite-oxidation of 3,6-diacetyl-9-ethylcarbazole; this acid had already been prepared by Gilman and Kirby (12) by oxidation of the diketone (XVII) with potassium ferricyanide.

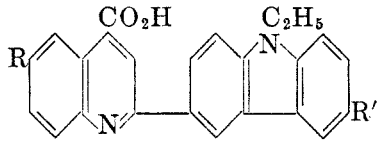
With respect to nitrogen-containing substituents, the oxime of 3-acetyl-9-

ethylcarbazole smoothly underwent a Beckmann rearrangement on treatment with phosphorus pentachloride in ether, yielding 3-acetamido-9-ethylcarbazole (X) (17), an analog of the carcinogenic 2-acetamidofluorene, and a homolog of 3-acetamidocarbazole (10). The oxime of 3-propionyl-9-ethylcarbazole (8) similarly yielded N-9-ethylcarbazol-3-ylpropionamide (XI). 3-ω-Chloroacetyl-9-ethylcarbazole (IX), prepared from 9-ethylcarbazole, chloroacetyl chloride, and aluminum chloride in the usual way, reacted with α-picoline to give a quaternary α-picolinium derivative which readily underwent the Tschitschibabin reaction (11) under the influence of sodium bicarbonate to give 2-(9′-ethylcarbazol-3′-yl)pyrrocoline (XXIV).



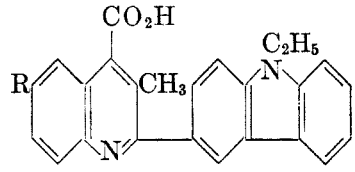
(XXIV)

The well-known ability of atophan (2-phenylcinchoninic acid) to produce under certain conditions the so-called "yellow atrophy" of the liver (13) suggests that some cinchoninic acids bearing polycyclic substituents in the 2-position might well show a similar toxicity. This has lead to the synthesis of a certain number of quinoline derivatives with a carbazole nucleus in the 2-position, some of them bearing nuclear halogen atoms, which are known to enhance the physiological properties of certain quinolines and acridines such as their antimalarial (14) or their strychnine-like activity (15). 3-Chloro-6-acetyl-9-ethylcarbazole



XXV R = H, R′ = Cl
XXVI R = Br, R′ = Cl
XXVII R = Br, R′ = H

(8) underwent a Pfitzinger reaction with isatin to give 2-(3′-chloro-9′-ethylcarbazol-3′-yl)cinchoninic acid (XXV), which could be decarboxylated by heat to 2-(3′-chloro-9′-ethylcarbazol-3′-yl)quinoline; the same ketone gave with 5-bromoisatin 6-bromo-2-(3′-chloro-9′-ethylcarbazol-3′-yl)cinchoninic acid (XXVI); from 5-bromoisatin and 3-acetyl-9-ethylcarbazole, 6-bromo-2-(9′-ethylcarbazol-3′-yl)cinchoninic acid (XXVII) was similarly obtained. Whereas 3-propionyl-9-ethylcarbazole readily underwent Pfitzinger reac-



XXVIII R = H
XXIX R = Br

tions with 5-bromoisatin and isatin, to give 6-bromo-3-methyl-(XXIX) and 3-methyl-2-(9′-ethylcarbazol-3′-yl)cinchoninic acid (XXVIII) respectively, no noticeable reaction occurred with 3-*n*-butyroyl-9-ethylcarbazole (V). Such inability in certain ketones to undergo the Pfitzinger reaction has already been repeatedly reported and discussed by the present authors (16).

Acknowledgment. This work has been carried out with the financial support of the U. S. Public Health Service (Federal Security Agency); the authors wish to express their thanks to the authorities concerned. Our thanks are also due to Miss Patricia F. Boshell, M.A. (Oxon.) for her assistance.

EXPERIMENTAL

Preparation of intermediates. The procedure for acetylation of 9-ethylcarbazole (8) previously described was altered as follows: to an ice-cooled solution of 40 g. of 9-ethylcarbazole and 22 g. of acetyl chloride in 300 ml. of pure dry benzene, 30 g. of finely powdered aluminum chloride was added in small portions with stirring. The mixture, which soon developed a dark green halochromic coloration, was poured on to ice after five hours at ordinary temperature. A solid precipitate was filtered off, and yielded after crystallization from benzene *3,6-diacetyl-9-ethylcarbazole* (4 g.); the benzene layer was washed with water and the solvent removed by distillation. The residue was vacuum-distilled; 26 g. of *3-acetyl-9-ethylcarbazole*, b.p. *circa* 255–260° at 18 mm., m.p. 115°, was obtained; 2 g. of 3,6-diacetyl-9-ethylcarbazole was recovered from the higher-boiling fraction.

Dry benzene was also preferred to carbon disulfide as a solvent in the preparation of *3-chloro-6-acetyl-9-ethylcarbazole* and of *3-propionyl-9-ethylcarbazole*, both of which were obtained in similar yields to the above.

3,9-Diethylcarbazole (II). A mixture of 30 g. of 3-acetyl-9-ethylcarbazole, 150 g. of granulated amalgamated zinc, 50 ml. of toluene, and 300 ml. of conc'd hydrochloric acid (*d*, 1.19) was refluxed for ten days with the daily addition of 50 ml. of hydrochloric acid. After addition of toluene, and shaking, the organic layer was decanted, washed with water, the solvent removed, and the residue vacuum-distilled. The yield was 20 g. of a rather mobile, pale yellow oil, b.p. 208–212° at 12 mm., which solidified after some standing. Recrystallization from petroleum ether (very soluble) yielded large colorless prisms, m.p. 45°, which gave with sulfuric acid a dark green coloration.

Anal. Calc'd for $C_{16}H_{17}N$: N, 6.0. Found: N, 6.2.

6-Bromo-3,9-diethylcarbazole (XVI). A solution of 9 g. of 3,9-diethylcarbazole in 100 ml. of acetic acid was treated with a solution of 6.5 g. of bromine in 20 ml. of acetic acid in small portions at room temperature. After a short heating on the water-bath, the mixture was poured into water, and the reaction product extracted with benzene. The benzene layer was worked up as usual, yielding on vacuum-distillation 6 g. of a pale yellow, viscous oil b.p. 250° at 15 mm.

Anal. Calc'd for $C_{16}H_{16}BrN$: N, 4.6. Found: N, 4.3.

3,6,9-Triethylcarbazole (XVIII). A mixture of 6 g. of 3,6-diacetyl-9-ethylcarbazole, 75 g. of amalgamated zinc, 5 ml. of xylene, and 150 ml. of conc'd hydrochloric acid was refluxed for seven days with frequent addition of further hydrochloric acid. The reaction product was worked up in the usual way, giving 4 g. of a pale yellow, mobile oil, b.p. 235° at 13 mm., which turned brown rapidly in the air.

Anal. Calc'd for $C_{18}H_{21}N$: N, 5.5. Found: N, 5.6.

This substance gave with picric acid a rather unstable *addition compound* which crystallized from ethanol in long silky brown-red needles, m.p. 158°.

3-Isobutyroyl-9-ethylcarbazole (III). To a solution of 9-ethylcarbazole (7.5 g.) and isobutyroyl chloride (5 g.) in dry benzene (100 ml.), aluminum chloride (5 g.) was added at room temperature with frequent shaking. After two days, the mixture was poured onto ice and the reaction product treated in the usual way, giving 7 g. of a thick, pale yellow oil, b.p. 270° at 13 mm., which did not solidify even after one year.

Anal. Calc'd for $C_{18}H_{19}NO$: N, 5.2. Found: N, 5.2.

3-Isobutyl-9-ethylcarbazole (IV). The foregoing ketone (6.5 g.) was refluxed for seven days with 50 g. of amalgamated zinc, 10 ml. of xylene, and 100 ml. of hydrochloric acid in the usual way; the reaction product, obtained in poor yield (2 g.), was a viscous pale yellow oil, b.p. 240–245° at 15 mm., n^{27} 1.6140, giving a deep red picrate.

Anal. Calc'd for $C_{18}H_{21}N$: N, 5.4. Found: N, 5.6.

n-Butyroylation of 9-ethylcarbazole. A mixture of 7.5 g. of 9-ethylcarbazole and 4.8 g. of *n*-butyroyl chloride in 150 ml. of benzene was treated with 6 g. of aluminum chloride in small portions, then left for two days. The reaction product was worked up in the usual way and yielded 7 g. of *3-n-butyroyl-9-ethylcarbazole* (V), b.p. 285–287° at 19 mm., crystallizing from methanol in long colorless needles, m.p. 86°.

Anal. Calc'd for $C_{18}H_{19}NO$: N, 5.2. Found: N, 5.1.

Repeated crystallization of the higher-boiling fraction from methanol (charcoal) gave 1.5 g. of *3,6-di-n-butyroyl-9-ethylcarbazole* (XIX) in the form of fine colorless prisms, m.p. 117–118°, giving with sulfuric acid a deep green coloration.

Anal. Calc'd for $C_{22}H_{25}NO_2$: N, 4.1. Found: N, 4.2.

n-Octanoyl-9-ethylcarbazole (VI). Prepared from 9-ethylcarbazole (10 g.) *n*-octanoyl chloride (10 g.) and aluminum chloride (10 g.) in benzene as in the previous example; it had b.p. 315–320° at 13 mm., and crystallized from ethanol or acetone in fine colorless glinting prisms, m.p. 83°.

Anal. Calc'd for $C_{22}H_{27}NO$: N, 4.3. Found: N, 4.5.

Recrystallization of the higher-boiling fraction from ethanol gave 0.5 g. of colorless needles melting over a wide range, and believed to be impure 3,6-di-*n*-octanoyl-9-ethylcarbazole.

Phenacetylation of 9-ethylcarbazole. To an ice-cooled solution of 20 g. of 9-ethylcarbazole and 20 g. of phenacetyl chloride in 200 ml. of carbon disulfide was added 20 g. of aluminum chloride; after six hours at room temperature, the mixture was poured onto ice; the solid portion was washed with water, dried, and recrystallized from benzene, giving 12.5 g. of *3,6-diphenacetyl-9-ethylcarbazole* (XX) in the form of fine colorless needles, m.p. 160°. Sulfuric acid gave a yellow-green halochromic coloration.

Anal. Calc'd for $C_{30}H_{25}NO_2$: N, 3.2. Found: N, 3.5.

The carbon disulfide layer was washed with alkaline water, dried over sodium sulfate, the solvent removed, and the residue vacuum-distilled. Yield, 8 g. of *3-phenacetyl-9-ethylcarbazole* (VII), b.p. 335–340° at 20 mm.; after crystallization from ethanol this formed fine colorless prisms, m.p. 105°, giving with sulfuric acid a brown-yellow coloration which rapidly turned leaf-green.

Anal. Calc'd for $C_{22}H_{19}NO$: N, 4.4. Found: N, 4.5.

3,6-Di-(β-phenylethyl)-9-ethylcarbazole (XXI). The ketone XX (10 g.) reduced in the usual way with amalgamated zinc and hydrochloric acid for three weeks, yielded 5 g. of compound XXI, b.p. 350–355° at 13 mm., which crystallized from ethanol in colorless, lustrous leaflets m.p. 112°, giving with sulfuric acid yellow-green coloration.

Anal. Calc'd for $C_{30}H_{29}N$: N, 3.4. Found: N, 3.1.

α,β-Diphenyl-β-(9-ethylcarbazol-3-yl)ethylene (XIV). To a solution of benzylmagnesium chloride made up from 13 g. of benzyl chloride and 2.5 g. of magnesium in anhydrous ether, 8 g. of 3-benzoyl-9-ethylcarbazole [prepared according to (8)] dissolved in several ml. of ether was added; the mixture was refluxed for 30 minutes, cooled, and decomposed with ice-cooled dilute sulfuric acid. The organic layer was washed with water, dried over sodium sulfate, the solvent removed, and the residue vacuum-distilled. Yield, 8 g. of the ethylene compound (XIV), b.p. 350–355° at 17 mm. (no decomposition), which gave with sulfuric acid a deep cherry-red coloration.

Anal. Calc'd for $C_{28}H_{23}N$: N, 3.7. Found: N, 3.6.

This substance solidified after some standing in ethanol, and crystallized from the latter solvent in the form of yellowish prisms which jellified *circa* 70°; this jelly liquefied around 100°. This behavior might be attributed to the presence of two stereoisomers.

3-Anisoyl-9-ethylcarbazole (VIII). An ice-cooled, well stirred solution of 20 g. of 9-ethylcarbazole and 19 g. of anisoyl chloride in 200 ml. of benzene was treated with 15 g. of aluminum chloride in small portions, and then kept for 16 hours at room temperature. On vacuum-distillation of the reaction product, 22 g. of ketone (VIII), b.p. *circa* 345° at 25 mm. was obtained; recrystallization from benzene gave glinting, colorless needles m.p. 154°,

sparingly soluble in ethanol, and forming an unstable orange-red addition-compound with picric acid.

Anal. Calc'd for $C_{22}H_{19}NO_2$: N, 4.2. Found: N, 4.1.

α-Phenyl-β-anisyl-β-(9-ethylcarbazol-3-yl)ethylene (XV). Prepared from the above ketone (10 g.) and benzylmagnesium chloride (made from 11 g. of benzyl chloride and 2.5 g. of magnesium) as for compound XIV; on vacuum-distillation, 12 g. of a thick, pale-yellow jelly b.p. 355–360° at 17 mm. was obtained which gave with sulfuric acid a deep lilac coloration. This substance solidified on long standing in ethanol, and crystallized from the latter solvent in fine yellowish needles which gelled at 80–85°, with total liquefication above 100°. As in the case of compound (XIV), this might be due to stereoisomerism.

Anal. Calc'd for $C_{29}H_{25}NO$: N, 3.5. Found: N, 3.3.

9-Ethylcarbazole-3-carboxylic acid (XII). A solution of 3-acetyl-9-ethylcarbazole in dioxane was stirred with an aqueous solution of sodium hypobromite made from 27 g. of sodium hydroxide (dissolved in 80 ml. of water), 14 ml. of bromine, and 100 g. of ice. After some gentle heating on a water-bath, the mixture was left overnight, the bromoform removed, and the filtered aqueous layer acidified with dilute hydrochloric acid. The precipitate was purified by solution in aqueous soda and reacidification. Recrystallization from acetic acid gave 16 g. of pale yellow, microscopic needles m.p. 225° (sublimes above 213°) which gave a greenish-blue coloration with sulfuric acid. Literature m.p. 226° Treatment with an excess of thionyl chloride yielded a solid *acid chloride* which reacted with ice-cooled conc'd ammonia to give *9-ethylcarbazole-3-carboxamide* (XIII), which from ethanol gave cream-yellow needles darkening above 192°, and melting around 222°.

Anal. Calc'd for $C_{15}H_{14}N_2O$: N, 11.7. Found: N, 11.9.

The *anilide* and the *p-toluidide*, prepared from the acid chloride and the corresponding amines in pyridine medium, both formed from ethanol cream-yellow microcrystalline powders melting over a wide range.

6-Bromo-9-ethylcarbazole-3-carboxylic acid (XXII). A suspension of 4 g. of the above acid in acetic acid was treated with a solution of 2.8 g. of bromine in acetic acid at room temperature; the mixture was left overnight, diluted with water, the precipitate collected, and recrystallized from acetic acid; an almost quantitative yield of the bromo-acid (XXII) was obtained in the form of a yellowish, microcrystalline powder m.p. 240–242° (decomp.) which gave a faint leaf-green coloration with sulfuric acid, and a solid acid chloride with thionyl chloride.

Anal. Calc'd for $C_{15}H_{12}BrNO_2$: N, 4.4. Found: N, 4.1.

9-Ethylcarbazole-3,6-dicarboxylic acid (XXIII). This acid (6.5 g.) was obtained by oxidizing 3,6-diacetyl-9-ethylcarbazole (7.5 g.) with sodium hypobromite (made from 18 g. of sodium hydroxide and 9 ml. of bromine) in the presence of dioxane in the usual way. It crystallized from a large quantity of acetic acid in microscopic cream-yellow needles m.p. > 330°, giving with sulfuric acid a jade-green coloration. Literature m.p. > 320°.

3-Acetamido-9-ethylcarbazole (X). The *oxime* of 3-acetyl-9-ethylcarbazole (20 g.), prepared by refluxing the ketone (18.5 g.) with hydroxylamine hydrochloride (16 g.) and sodium carbonate (10 g.) in aqueous ethanol, crystallized from methanol in colorless leaflets, m.p. 175–176° giving a transient green coloration with sulfuric acid.

Anal. Calc'd for $C_{16}H_{16}N_2O$: N, 11.1. Found: N, 11.2.

Finely powdered phosphorus pentachloride (17 g.) was stirred into an ice-cooled suspension of the oxime (19 g.) in anhydrous ether; stirring was continued for some minutes at room temperature, and the mixture was then poured onto ice. The solid precipitate was filtered off, thoroughly washed with an aqueous solution of sodium carbonate and then with water, dried, and recrystallized twice from a mixture of ethanol and benzene. Yield, 12 g. of glinting, colorless prisms m.p. 203–204°, which reddened on exposure to air, and gave a deep greenish-blue coloration with sulfuric acid. Lindemann (17) gives m.p. 190°.

Anal. Calc'd for $C_{16}H_{16}N_2O$: N, 11.1. Found: N, 10.8.

Heating the *amide* with conc'd hydrochloric acid for three hours yielded the sparingly soluble *3-amino-9-ethylcarbazole hydrochloride* from which, on treatment with ammonia

the free *amine* was obtained; this gave with 2,3-dichloro-1,4-naphthoquinone (14) a violet-black compound which gave deep red solutions in acetic acid.

3,6-Diacetyl-9-ethylcarbazole dioxime. This compound, prepared from 3,6-diacetyl-9-ethylcarbazole and hydroxylamine in the usual way, formed a colorless microcrystalline powder, m.p. 230–232° (decomp.) from ethanol.

Anal. Calc'd for $C_{18}H_{19}N_3O_2$: N, 13.6. Found: N, 13.3.

N-9-Ethylcarbazol-3-ylpropionamide (XI). The *oxime* of 3-propionyl-9-ethylcarbazole prepared as above, crystallized from ethanol in fine colorless needles, m.p. 137–138°.

Anal. Calc'd for $C_{17}H_{18}N_2O$: N, 10.5. Found: N, 10.4.

The Beckman rearrangement gave *N-9-ethylcarbazol-3-ylpropionamide* in the form of long, glinting colorless needles (from ethanol) m.p. 172°, giving a deep blue coloration with sulfuric acid, and a deep red picrate.

Anal. Calc'd for $C_{17}H_{18}N_2O$: N, 10.5. Found: 10.2.

3-n-Octanoyl-9-ethylcarbazole oxime. Prepared as above, it formed lustrous, silky colorless needles, m.p. 130° from ethanol.

Anal. Calc'd for $C_{22}H_{28}N_2O$: N, 8.3. Found: N, 8.1.

3-ω-Chloroacetyl-9-ethylcarbazole (IX). Prepared in the usual way from 9-ethylcarbazole (30 g.), chloroacetyl chloride (20 g.), and aluminum chloride (21 g.) in benzene, it was isolated by vacuum-distillation (b.p. *circa* 280–285° at 2 mm.), and formed long, glistening yellow-tinged needles, m.p. 115–116° (yield, 7 g.) from ethanol.

Anal. Calc'd for $C_{16}H_{14}ClNO$: N, 5.1. Found: N, 5.0.

2-(9'-Ethylcarbazol-3'-yl)pyrrocoline (XXIV). The chloroacetyl compound (1 g.) and 5 g. of anhydrous α-picoline were gently refluxed for three hours. After cooling, dry ether was added, the insoluble quaternary adduct dissolved in hot water without further purification, and sodium bicarbonate added to this solution. After a few minutes boiling, the pyrrocoline precipitated; it formed long, silky glistening colorless needles, m.p. 198° from benzene giving with sulfuric acid a deep blue coloration, and with hydrogen chloride a yellow one.

Anal. Calc'd for $C_{21}H_{18}N_2$: N, 9.3. Found: N, 9.0.

2-(3'-Chloro-9'-ethylcarbazol-3'-yl)cinchoninic acid (XXV). A mixture of 2 g. of 3-chloro-6-acetyl-9-ethylcarbazole, 1.1 g. of isatin, and 1.3 g. of potassium hydroxide dissolved in 2 ml. of water and 15 ml. of ethanol was refluxed for two days; the reaction product was diluted with water, and the neutral impurities removed by extraction with ether. The aqueous layer on acidification gave an orange-yellow precipitate (2.5 g.) which formed orange-yellow microcrystals m.p. *circa* 228–233° (decomp.) from a large amount of acetic acid.

Anal. Calc'd for $C_{24}H_{17}ClN_2O_2$: N, 6.9. Found: N, 7.0.

This substance, on heating *in vacuo* above its m.p. and purification of the resulting base through the *picrate*, gave *2-(3'-chloro-9'-ethylcarbazol-3'-yl)quinoline* in the form of faintly yellow needles (from a mixture of ethanol and benzene) m.p. 161°.

Anal. Calc'd for $C_{23}H_{17}ClN_2$: N, 7.8. Found: N, 7.5.

6-Bromo-2-(3'-chloro-9'-ethylcarbazol-3'-yl)cinchoninic acid (XXVI). Prepared as above from 3 g. of 3-chloro-6-acetyl-9-ethylcarbazole, 2.5 g. of 5-bromoisatin, and 2 g. of potassium hydroxide (yield, 5.2 g.); crystallized from a large amount of acetic acid in microscopic orange needles melting with decomposition above 280°.

Anal. Calc'd for $C_{24}H_{16}BrClN_2O_2$: N, 5.8. Found: N, 5.5.

6-Bromo-2-(9'-ethylcarbazol-3'-yl)cinchoninic acid (XXVII). Obtained in quantitative yield from 3-acetyl-9-ethylcarbazole (4 g.), 5-bromoisatin (4 g.), and potassium hydroxide (3 g.); from a large amount of acetic acid it gave orange-yellow microscopic needles, m.p. *circa* 272–275°.

Anal. Calc'd for $C_{24}H_{17}BrN_2O_2$: N, 6.3. Found: N, 6.0.

3-Methyl-2-(9'-ethylcarbazol-3'-yl)cinchoninic acid (XXVIII). From 4 g. of 3-propionyl-9-ethylcarbazole, 2.5 g. of isatin, and 3 g. of potassium hydroxide; from acetic acid it gave fine bright yellow needles (4 g.) m.p. > 310°.

Anal. Calc'd for $C_{25}H_{20}N_2O_2$: N, 7.3. Found: N, 7.2.

6-Bromo-3-methyl-2-(9'-ethylcarbazol-3'-yl)cinchoninic acid (XXIX). From 4 g. of 3-

propionyl-9-ethylcarbazole, 4 g. of 5-bromoisatin, and 3 g. of potassium hydroxide, there was obtained 5 g. of an acid which gave fine bright yellow microcrystals, m.p. 310° from nitrobenzene.

Anal. Calc'd for $C_{25}H_{19}BrN_2O_2$: N, 6.1. Found: N, 6.0.

SUMMARY

Several derivatives of 9-ethylcarbazole having substituents in the 3- and 6-positions have been prepared for biological investigation.

PARIS V, FRANCE

REFERENCES

(1) See, for instance, FIESER, *Am. J. Cancer*, **34**, 37 (1934); HARTWELL, *Survey of Compounds which have been tested for Carcinogenic Activity*, National Cancer Institute, U. S. Public Health Service, Washington, D. C.
(2) BONSER, *J. Path. Bact.*, **55**, 1 (1943).
(3) DITTMAR, *Z. Krebsforsch.*, **52**, 17 (1941).
(4) WILSON, DE EDS, AND COX, *Cancer Research*, **1**, 595 (1941); SHEAR, cited by BIELSCHOWSKY, *Brit. Med. Bull.*, **4**, 383 (1947).
(5) LACASSAGNE, BUU-HOÏ, ROYER, AND ZAJDELA, *Compt. rend. soc. biol.*, **141**, 635 (1947).
(6) BOYLAND AND BRUES, *Proc. Roy. Soc. (London)*, **B122**, 429 (1937).
(7) *Ann. Rep. British Empire Cancer Campaign*, **25**, 154 (1947).
(8) BUU-HOÏ AND ROYER, *Rec. trav. chim.*, **66**, 533 (1947).
(9) *Ann. Rep. British Empire Cancer Campaign*, **25**, 37 (1947).
(10) ULLMANN, *Ann.*, **332**, 93 (1904).
(11) TSCHITSCHIBABIN, *Ber.*, **60**, 1607 (1927).
(12) GILMAN AND KIRBY, *J. Org. Chem.*, **1**, 146 (1936); GILMAN AND SPATZ, *J. Am. Chem. Soc.*, **63**, 1553 (1941).
(13) GOODMAN AND GILMAN, *The Pharmacological Basis of Therapeutics*, MacMillan, New York, N. Y., 1941, p. 235.
(14) MAGIDSON, *et al.*, *Ber.*, **69**, 396, 537 (1936).
(15) VON BRAUN, *Ann*, **451**, 1 (1926).
(16) BUU-HOÏ, *et al.*, *Bull. soc. chim.*, **13**, 123, 134, 374 (1946); *J. Chem. Soc.*, 795 (1946), 106 (1948); *Compt. rend.*, **227**, 1251, 1377 (1948).
(17) LINDEMANN, *Ber.*, **57**, 555 (1924).