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

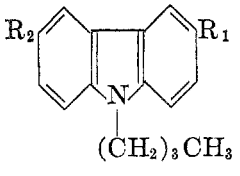
POTENTIAL NITROGEN-HETEROCYCLE CARCINOGENS. XI. SUBSTITUTION REACTIONS OF N-ALKYLCARBAZOLES[1]

NG. PH. BUU-HOÏ AND RENÉ ROYER

Received February 9, 1951

In continuation of our earlier investigations of the synthesis of new derivatives of carbazole to be used for cancer research (1), the reactivity of several N-alkylcarbazoles towards various substitution-reagents has now been more thoroughly explored. The N-alkylcarbazoles used for this purpose were the N-ethyl, N-*n*-butyl, and N-isoamyl derivatives; in addition to these intermediates, N-benzylcarbazole was also studied. The N-alkyl- and N-aralkylcarbazoles were preferred to carbazole itself as a starting point for such syntheses because of the lower melting points and higher solubility in organic solvents of their reaction products—circumstances which facilitate biological research. Emphasis has been laid on the synthesis of compounds bearing halogen atoms or nitro groups, in view of the increased toxicity to liver tissue developed in organic molecules by halogenation or nitration.

The chlorination of N-*n*-butylcarbazole with sulfuryl chloride in chloroform yielded, according to the experimental conditions, either a trichloro compound [probably 1,3,6-trichloro-9-*n*-butylcarbazole (XII)] or a mixture of 3-chloro-9-*n*-butylcarbazole (I) and 3,6-dichloro-9-*n*-butylcarbazole (II). Mono- and di-chlorination of carbazole (2) and N-ethylcarbazole (3) have been readily performed with sulfuryl chloride, but no trichloro derivatives have yet been obtained in this manner; trichlorination of carbazole, however, has been effected with chlorine itself (4). Halogenation of N-*n*-butylcarbazole by bromine in acetic

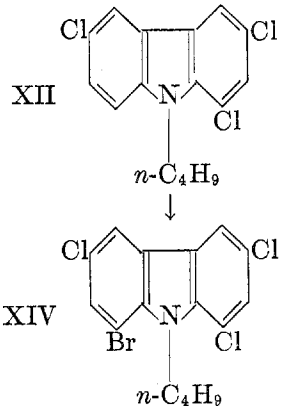


I $R_1 = Cl, R_2 = H$
II $R_1 = R_2 = Cl$
III $R_1 = Br, R_2 = H$
IV $R_1 = R_2 = Br$
V $R_1 = NO_2, R_2 = H$
VI $R_1 = Br, R_2 = NO_2$
VII $R_1 = NH_2, R_2 = H$
VIII $R_1 = R_2 = COCH_3$
IX $R_1 = COCH_3, R_2 = Cl$
X $R_1 = COCH_2C_6H_5, R_2 = H$
XI $R_1 = COCH_2C_6H_5, R_2 = Cl.$

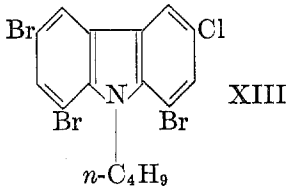
acid yielded a mixture of 3-bromo- (III) and 3,6-dibromo-9-*n*-butylcarbazole (IV). It is of interest that bromination of 3-chloro-9-*n*-butylcarbazole introduced three bromine atoms, probably giving 1,6,8-tribromo-3-chloro-9-*n*-butylcarbazole (XIII), and that 1,3,6-trichloro-9-*n*-butylcarbazole reacted with bromine to add one bromine atom, giving, apparently, 1,3,6-trichloro-8-bromo-9-*n*-butylcarbazole (XIV). 3-Bromo-9-ethylcarbazole, on the other hand, gave with sulfuryl chloride 1,6,8-trichloro-3-bromo-9-ethylcarbazole (XV). These findings seem to be in line with an early observation by Votoček (5) that, with an excess

[1] Paper X in this series: Buu-Hoï, Khôi, and Xuong, *J. Org. Chem.*, **16**, 315 (1951).

of bromine, carbazole gave a tetrasubstituted compound, apparently 1,3,6,8-tetrabromocarbazole.

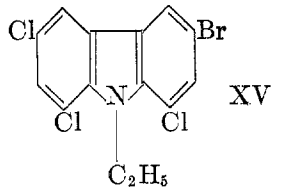


XII



XIII

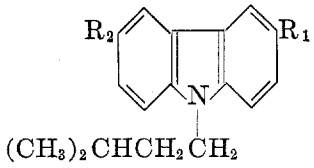
XIV



XV

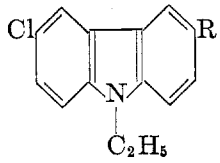
Whilst halogenation thus leads preferentially to polysubstitution, nitration of N-*n*-butylcarbazole under normal conditions gave only the 3-nitro derivative (V), which was easily reduced with stannous chloride to 3-amino-9-*n*-butylcarbazole (VII), an interesting compound for cancer research in view of its analogy with 2-aminofluorene. From compound III, 3-bromo-6-nitro-9-*n*-butylcarbazole (VI) was easily prepared.

Friedel-Crafts reactions with N-*n*-butylcarbazole yielded a mono- or a disubstitution product, according to the nature of the acid chloride used. Thus, with acetyl chloride, the only isolated product was 3,6-diacetyl-9-*n*-butylcarbazole (VIII), whereas with the somewhat less reactive α-toluyl chloride, 3-(α-toluyl)-9-*n*-butylcarbazole (X) was easily obtained. Similarly, N-isoamylcarbazole was chiefly acetylated to the corresponding diketone (XVI), but yielded on α-toluylation 3-(α-toluyl)-9-isoamylcarbazole (XVII). It should be mentioned



XVI $R_1 = R_2 = COCH_3$
XVII $R_1 = COCH_2C_6H_5$, $R_2 = H$

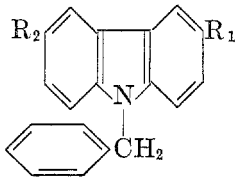
that when one of the two main reactive positions 3 and 6 was blocked, N-alkylcarbazoles gave only monosubstitution products in Friedel-Crafts reactions: thus, 3-chloro-9-*n*-butylcarbazole gave on acetylation and α-toluylation 3-acetyl- (IX) and 3-(α-toluyl)-6-chloro-9-*n*-butylcarbazole (XI). 3-Chloro-9-ethylcarbazole was likewise easily acylated to 3-propionyl- (XVIII), 3-*n*-butyryl- (XIX),



XVIII $R = COCH_2CH_3$
XIX $R = CO(CH_2)_2CH_3$
XX $R = COC_6H_5$
XXI $R = NHCOCH_3$
XXII $R = NHCOC_2H_5$

and 3-benzoyl-6-chloro-9-ethylcarbazole (XX); 3-bromo-9-ethylcarbazole could also be converted to 3-acetyl-6-bromo-9-ethylcarbazole. 3-Acetamino- (XXI) and 3-propionylamino-6-chloro-9-ethylcarbazole (XXII), prepared by Beckmann rearrangement of the oximes of the parent ketones, is of interest for research on cancer of the liver.

In respect to reactivity, N-benzylcarbazole does not differ from N-alkylcarbazoles; thus, the action of sulfuryl chloride gave 3,6-dichloro-9-benzylcarbazole (XXIII), and that of bromine, 3,6-dibromo-9-benzylcarbazole (XXIV), whereas



XXIII $R_1 = R_2 = Cl$
XXIV $R_1 = R_2 = Br$
XXV $R_1 = NO_2, R_2 = H$
XXVI $R_1 = COCH_3, R_2 = H$
XXVII $R_1 = R_2 = COCH_3$

nitration yielded 3-nitro-9-benzylcarbazole (XXV). Acetylation gave both 3-acetyl- (XXVI) and 3,6-diacetyl-9-benzylcarbazole (XXVII).

Acknowledgement. This work was supported in part by the U. S. Public Health Service, Federal Security Agency; the authors wish to thank the authorities concerned.

EXPERIMENTAL (with M. Hubert-Habart)

N-Alkylation of carbazole. N-*n*-Butylcarbazole was obtained in good yield by a variation of the directions given in the literature (6): a solution of 50 g. of carbazole in 250 ml. of dry toluene was refluxed with 14.5 g. of finely powdered sodium amide until evolution of ammonia ceased. After cooling, 82 g. of *n*-butyl bromide was added, and the mixture refluxed for 48 hours; after cooling again, water was carefully added, the toluene layer separated and washed with water, then dried over sodium sulfate, and the toluene removed in a vacuum. The residue gave on vacuum-distillation 46 g. of a product b.p. 218–219°/19 mm. which consisted of N-*n*-butylcarbazole mixed with some unreacted carbazole. This latter (2 g.) was removed by treatment with light petroleum ether which dissolved only N-*n*-butylcarbazole, m.p. 58°; yield: 44 g. N-Isoamylcarbazole was similarly prepared from 30 g. of carbazole, 8.5 g. of sodium amide, and 55 g. of isoamyl bromide; yield, 36 g. of a product b.p. 230–232°/29 mm., crystallizing from petroleum ether in colorless prisms, m.p. 44°. This compound was described in the literature (6) as an oil.

N-Benzylcarbazole was obtained from benzyl chloride in the same way, except that separation from the unreacted carbazole was achieved through vacuum-distillation; N-benzylcarbazole boiled at 267–268°/24 mm., and melted at 112–113°. Literature values, m.p. 114° (6) and 118–120° (7).

Chlorination of N-n-butylcarbazole. (a) To 4.5 g. of the carbazole in 50 ml. of chloroform, was added 3 g. of sulfuryl chloride all at once. After the lively reaction had subsided, the mixture was refluxed for 30 minutes on a water-bath and poured into water. The chloroform layer was washed with an aqueous sodium hydroxide, with water, and dried over sodium sulfate. After removal of the solvent and vacuum-distillation of the residue, the portion boiling at 276–278°/19 mm. (4.5 g.) was collected, and gave, after several recrystallizations from methanol, *1,3,6-trichloro-9-n-butylcarbazole* (XII) in the form of fine colorless needles m.p. 71–72°, giving no coloration with sulfuric acid.

Anal. Calc'd for $C_{16}H_{14}Cl_3N$: C, 58.8; H, 4.3.
Found: C, 58.5; H, 4.3.

(b) To an ice-cooled solution of 22.5 g. of N-*n*-butylcarbazole in 150 ml. of chloroform,

was added 15 g. of sulfuryl chloride in small portions; the mixture was kept at room temperature for 15 minutes, then refluxed for ten minutes, and worked up as above. The portion boiling at 240–250°/15 mm. crystallized partially after prolonged standing at room temperature; the solid was separated, and the oily part redistilled. Yield, 22 g. of *3-chloro-9-n-butylcarbazole* (I), forming a pale yellow viscous oil boiling at 240–245°/15 mm., which set in the refrigerator into a white solid.

Anal. Calc'd for $C_{16}H_{16}ClN$: C, 74.5; H, 6.2.
Found: C, 74.1; H, 6.0.

The portion boiling at 250–260°/15 mm. (3 g.) was mainly *3,6-dichloro-9-n-butylcarbazole* (II), and crystallized from ligroin in long transparent prisms, or from methanol in silky colorless needles, m.p. 68°.

Anal. Calc'd for $C_{16}H_{15}Cl_2N$: C, 65.8; H, 5.1.
Found: C, 66.1; H, 5.0.

Bromination of N-n-butylcarbazole. To an ice-cooled solution of 20 g. of N-*n*-butylcarbazole in acetic acid, 14.5 g. of bromine was carefully added dropwise with shaking. After 15 minutes at room temperature, the reaction mixture was poured into water and extracted with benzene, the benzene layer was washed with dilute aqueous sodium hydroxide, with water, and dried over sodium sulfate. After removal of the solvent and vacuum-fractionation of the residue, 15 g. of *3-bromo-9-n-butylcarbazole* (III) was obtained as a yellow viscous oil, boiling at 260–265°/17 mm.

Anal. Calc'd for $C_{16}H_{16}BrN$: C, 63.5; H, 5.3.
Found: C, 63.2; H, 5.4.

The higher-boiling fraction (298–300°/23 mm.) consisted of *3,6-dibromo-9-n-butylcarbazole* (IV), which crystallized from methanol in shiny colorless needles, m.p. 72°. Yield, 11.5 g.

Anal. Calc'd for $C_{16}H_{15}Br_2N$: C, 50.4; H, 3.9.
Found: C, 50.1; H, 3.9.

1,6,8-Tribromo-3-chloro-9-n-butylcarbazole (XIII). 3-Chloro-9-*n*-butylcarbazole (3 g.) was treated with 2 g. of bromine in acetic acid in the usual way. The reaction mixture was poured into water, and the solid was recrystallized several times from acetone, giving clumps of fine colorless needles, m.p. 140°.

Anal. Calc'd for $C_{16}H_{13}Br_3Cl$: C, 38.8; H, 2.6.
Found: C, 39.1; H, 2.4.

1,6,8-Trichloro-3-bromo-9-n-butylcarbazole (XIV). 1,3,6-Trichloro-9-*n*-butylcarbazole (3 g.) was similarly treated with 2 g. of bromine. The reaction product, after several recrystallizations from ethanol, formed long silky colorless needles, m.p. 112°.

Anal. Calc'd for $C_{16}H_{13}BrCl_3N$: C, 47.3; H, 3.2.
Found: C, 47.3; H, 3.0.

1,6,8-Trichloro-3-bromo-9-ethylcarbazole (XV). A solution of 3 grams of 3-bromo-9-ethylcarbazole (3) and 1.7 g. of sulfuryl chloride in 30 ml. of chloroform was refluxed for 40 minutes on a water-bath. The solvent and the unreacted sulfuryl chloride were removed in a vacuum, and the solid residue was recrystallized several times from ethanol to give long shiny colorless needles, m.p. 133°.

Anal. Calc'd for $C_{14}H_9BrCl_3N$: C, 44.5; H, 2.4.
Calc'd for $C_{14}H_{10}BrCl_2N$: C, 48.9; H, 3.2.
Found: C, 44.0; H, 2.6.

3-Nitro-9-n-butylcarbazole (V). To an ice-cooled solution of 15 g. of N-*n*-butylcarbazole in acetic acid, 5 g. of fuming nitric acid (*d.* 1.49, dissolved in 10 ml. of acetic acid) was added dropwise with stirring. After one hour's standing, the reaction product was poured into water; the solid precipitate was collected, washed thoroughly with water, and recrystallized from acetic acid. The yield was 18 g. of large, shiny pale yellow leaflets, m.p. 98°, giving an intense violet coloration with sulfuric acid.

Anal. Calc'd for $C_{16}H_{16}N_2O_2$: C, 71.6; H, 6.0.
Found: C, 71.3; H, 5.9.

3-Amino-9-n-butylcarbazole (VII). To a solution of 4.5 g. of the above nitro compound in 100 ml. of hot ethanol, was added in small portions 19 g. of stannous chloride dissolved in concentrated hydrochloric acid. The mixture was subsequently boiled for some minutes; after cooling, the *chlorostannate* of the amine was filtred; it formed long shiny grayish needles. The free *amine*, obtained by treatment of this salt with an aqueous solution of potassium hydroxide, crystallized from benzene in fine grayish needles, m.p. 93°, giving with sulfuric acid a deep blue coloration.

Anal. Calc'd for $C_{16}H_{18}N_2$: N, 11.7. Found: N, 11.4.

This amine was further characterized by its reaction product with 2,3-dichloro-1,4-naphthoquinone (8); this formed deep violet needles from ethanol, giving with sulfuric acid a dark blue-violet coloration.

3-Bromo-6-nitro-9-n-butylcarbazole (VI). An ice-cooled solution of 3 g. of 3-bromo-9-*n*-butylcarbazole in acetic acid was nitrated in the usual way with 1 g. of fuming nitric acid. Yield, 3 g. of a mononitro compound crystallizing from acetic acid in fine yellow needles, m.p. 179–180°.

Anal. Calc'd for $C_{16}H_{15}BrN_2O_2$: C, 55.3; H, 4.3.
Found: C, 55.4; H, 4.4.

3,6-Diacetyl-9-n-butylcarbazole (VIII). To 10 g. of N-*n*-butylcarbazole, 4.5 g. of acetyl chloride, and 50 ml. of anhydrous benzene, 6 g. of finely powdered aluminum chloride was added in small portions with stirring. After 8 hours' standing at room temperature, the reaction product was worked up in the usual way, and gave on vacuum distillation 3 g. of a portion boiling above 300°/15 mm., which crystallized from ethanol in long, silky colorless needles, m.p. 129°, giving with sulfuric acid a greenish-yellow coloration.

Anal. Calc'd for $C_{20}H_{21}NO_2$: C, 78.1; H, 6.8.
Found: C, 78.1; H, 6.6.

3-(α-Toluyl)-9-n-butylcarbazole (X). A mixture of 10 g. of N-*n*-butylcarbazole and 7.5 g. of α-toluyl chloride in benzene was treated with 6 g. of aluminum chloride as above, resulting in a deep green halochromic coloration. After the usual treatment, 7.5 g. of a ketone boiling at 350°/20 mm. was obtained; this crystallized from ethanol in clumps of colorless needles, m.p. 102°, giving with sulfuric acid a brown-yellow color turning rapidly green.

Anal. Calc'd for $C_{24}H_{23}NO$: N, 4.1. Found: N, 4.0.

Acetylation of N-isoamylcarbazole. A benzene solution of 15 g. of N-isoamylcarbazole and 6.3 g. of acetyl chloride was treated with 10 g. of aluminum chloride in the usual way. On vacuum-distillation of the reaction product, a forerun, consisting of an oily portion (4 g.) boiling at about 300°/20 mm., was obtained. This gave an orange *picrate* m.p. 99°, and proved to be a monoketone by hypobromite oxidation to a monoacid, probably *9-isoamylcarbazole-3-carboxylic acid*, crystallizing from ethanol in fine colorless needles which darkened above 200° and were completely melted at about 226° (Neut. equiv., 276; Calc'd, 281). The higher-boiling portion (4.5 g.; > 305°/20 mm.) crystallized from methanol in tufts of silky colorless needles, m.p. 149°, giving a greenish-yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{21}H_{23}NO_2$: N, 4.3. Found: N, 4.2.

3-(α-Toluyl)-9-isoamylcarbazole (XVII). From 15 g. of N-isoamylcarbazole, 11 g. of α-toluyl chloride, and 10 g. of aluminum chloride in 200 ml. of benzene; after 12 hours' standing at room temperature, the reaction mixture was worked up in the usual way. Yield, 12 g. of a ketone, b.p. 346–348°/15 mm., crystallizing from ethanol in shiny colorless leaflets, m.p. 90°. This ketone gave no Pfitzinger reaction when heated for 24 hours with isatin in alkaline medium.

Anal. Calc'd for $C_{25}H_{25}NO$: C, 84.5; H, 7.0.
Found: C, 84.2; H, 7.1.

3-Acetyl-6-chloro-9-n-butylcarbazole (IX). To 15 g. of 3-chloro-9-*n*-butylcarbazole and 6 g. of acetyl chloride in 200 ml. of carbon disulfide (benzene as solvent proved unsatisfac-

tory), 9 g. of aluminum chloride was added with stirring and cooling in ice-water. The deep green mixture was kept overnight at room temperature and worked up in the usual ways giving 15 g. of a ketone, b.p. 290°/15 mm., which crystallized from ethanol in shiny colorless needles, m.p. 113°. The solution in sulfuric acid was orange-yellow.

Anal. Calc'd for $C_{18}H_{15}ClNO$: C, 72.1; H, 6.0.
Found: C, 72.0; H, 6.1.

This ketone gave a positive Pfitzinger reaction with isatin, a yellow cinchoninic acid being formed.

3-(α-Toluyl)-6-chloro-9-n-butylcarbazole (XI). Similarly obtained in 50% yield from 5 g. of 3-chloro-9-*n*-butylcarbazole, 3.5 g. of α-toluyl chloride, and 3 g. of aluminum chloride, it boiled at about 360°/16 mm., and crystallized from ethanol in fine shiny colorless needles, m.p. 151°.

Anal. Calc'd for $C_{24}H_{22}ClNO$: C, 76.7; H, 5.8.
Found: C, 76.9; H, 5.9.

Acetylation of 3-bromo-9-ethylcarbazole. This compound was prepared by adding dropwise a solution of 18.8 g. of bromine in 60 ml. of acetic acid to an ice-cooled solution of 23 g. of N-ethylcarbazole in 800 ml. of acetic acid; yield, 9 g. of a product boiling at 265–270°/18 mm. Acetylation, performed with 5 g. of this compound, 2 g. of acetyl chloride, and 3.5 g. of aluminum chloride in carbon disulfide, yielded 3 g. of *3-acetyl-6-bromo-9-ethylcarbazole*, b.p. about 300°/18 mm., which, after repeated crystallizations from ethanol, formed fine pale yellow needles, m.p. 132–133°, giving a brown-yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{16}H_{14}BrNO$: N, 4.4. Found: N, 4.6.

Acetylation of 3-chloro-9-ethylcarbazole. The acetylation was effected in better yield in benzene solution, thus varying the procedure described in the literature (3). *3-Acetyl-6-chloro-9-ethylcarbazole*, b.p. about 290°/20 mm., thus obtained, readily gave an *oxime* (11 g.) which was shaken for ten minutes with 8 g. of finely powdered phosphorus pentachloride in anhydrous ether. The reaction mixture was poured onto cracked ice, the ether allowed to evaporate, and the precipitate washed thoroughly with water. After two recrystallizations from ethanol, *3-acetamino-6-chloro-9-ethylcarbazole* was obtained as fine shiny colorless needles, which decomposed above 233°, and were completely melted at 245°.

Anal. Calc'd for $C_{16}H_{15}ClN_2O$: N, 9.8. Found: N, 9.6.

Furthermore the hypobromite oxidation of 3-acetyl-6-chloro-9-ethylcarbazole readily yielded *6-chloro-9-ethylcarbazole-3-carboxylic acid*, which formed grayish needles from ethanol, subliming above 240°, and melting at 254° (Neut. equiv., 270. Calc'd, 273.5).

3-Propionyl-6-chloro-9-ethylcarbazole (XVIII). Obtained from 12 g. of 3-chloro-9-ethylcarbazole, 6 g. of propionyl chloride, and 7 g. of aluminum chloride in benzene. Yield, 10 g. of a ketone, b.p. 306–309°/29 mm., crystallizing from ethanol in long shiny leaflets, m.p. 104°, giving with sulfuric acid an orange-yellow coloration.

Anal. Calc'd for $C_{17}H_{16}ClNO$: C, 71.4; H, 5.6.
Found: C, 71.3; H, 5.5.

The *oxime* crystallized from ethanol in shiny colorless needles, m.p. 170–172°.

Anal. Calc'd for $C_{17}H_{17}ClN_2O$: N, 9.3. Found: N, 9.2.

The Beckmann rearrangement of this oxime, conducted as for the lower homolog, gave *3-propionylamino-6-chloro-9-ethylcarbazole* (XXII), which crystallized from ethanol in fine colorless prisms, m.p. 204°.

Anal. Calc'd for $C_{17}H_{17}ClN_2O$: N, 9.3. Found: N, 9.1.

3-n-Butyryl-6-chloro-9-ethylcarbazole (XIX). From 7 g. of 6-chloro-9-ethylcarbazole, 3.5 g. of *n*-butyryl chloride, and 5 g. of aluminum chloride in benzene. Yield, 6 g. of a ketone boiling at about 300°/25 mm., crystallizing from ethanol in long shiny colorless needles, m.p. 100°.

Anal. Calc'd for $C_{18}H_{18}ClNO$: C, 72.1; H, 6.0.
Found: C, 72.0; H, 6.2.

A Friedel-Crafts reaction, similarly performed with 6-chloro-9-ethylcarbazole and

chloroacetyl chloride, gave a ketone crystallizing from ethanol in tufts of shiny colorless needles, m.p. 157–158°, giving with sulfuric acid an orange coloration. This was apparently *3-chloroacetyl-6-chloro-9-ethylcarbazole*, but the very poor yield prevented analytical proof.

3-Benzoyl-6-chloro-9-ethylcarbazole (XX). From 18 g. of the carbazole, 11 g. of benzoyl chloride, and 11 g. of aluminum chloride in benzene, the mixture being kept for three days at room temperature. Yield, 18 g. of a ketone, b.p. 342–344°/18 mm., crystallizing from ethanol in clumps of shiny colorless needles, m.p. 122°, giving with sulfuric acid an orange red coloration.

Anal. Calc'd for $C_{21}H_{16}ClNO$: C, 75.5; H, 4.7.
Found: C, 75.4; H, 4.8.

This ketone reacted with benzylmagnesium chloride in ether to give a carbinol which lost water on vacuum-distillation to form a pale yellow, resinous ethylene compound, apparently *α,β-diphenyl-β-(6-chloro-9-ethyl-3-carbazolyl)ethylene*, giving with sulfuric acid a deep red coloration (1).

Chlorination of N-benzylcarbazole. A cooled solution of 7 g. of this carbazole in 50 ml. of chloroform was treated with 3.7 g. of sulfuryl chloride in small portions, and the mixture subsequently refluxed for ten minutes. After evaporation of the solvent and vacuum-distillation of the residue, 10 g. of a product, b.p. 293–300°/15 mm., was obtained. This, on fractional crystallization from equal parts of ethanol and benzene, gave a more soluble part, melting over a wide range (100–107°); this fraction could not be further purified and was probably an impure monosubstitution product. The less soluble part (5 g.) formed long shiny colorless needles, m.p. 145°, and was *3,6-dichloro-9-benzylcarbazole* (XXIII).

Anal. Calc'd for $C_{19}H_{13}Cl_2N$: C, 70.0; H, 4.0.
Found: C, 70.3; H, 3.8.

Bromination of N-benzylcarbazole. A solution of 4.4 g. of bromine in 10 ml. of acetic acid was added dropwise to a cooled acetic acid solution of 7 g. of N-benzylcarbazole. The reaction product was poured into water, and the precipitate (4.5 g.) recrystallized several times from a mixture of ethanol and benzene. *3,6-Dibromo-9-benzylcarbazole* (XXIV) formed long silky colorless needles, m.p. 158°, giving almost no coloration with sulfuric acid.

Anal. Calc'd for $C_{19}H_{13}Br_2N$: C, 55.0; H, 3.1.
Found: C, 55.4; H, 3.4.

The mother liquors contained a substance melting at about 111°, which could not be purified.

Nitration of N-benzylcarbazole. N-Benzylcarbazole (3 g.) was nitrated in acetic acid with 1 g. of fuming nitric acid in the usual way. Yield, 2.2 g. of *3-nitro-9-benzylcarbazole*, crystallizing from acetic acid in tufts of long shiny greenish-yellow needles, m.p. 144°, giving a violet coloration with sulfuric acid.

Anal. Calc'd for $C_{19}H_{14}N_2O_2$: N, 9.2. Found: N, 9.0.

As a by-product, a compound insoluble in acetic acid was obtained, which crystallized from *o*-dichlorobenzene in fine yellow needles melting above 320°. The constitution of this compound could not be elucidated, nor could that of the nitration-product of 3,6-dibromo-9-benzylcarbazole (fine yellow needles, m.p. about 213–214°) which was obtained in a similar manner.

Acetylation of N-benzylcarbazole. From 15 g. of N-benzylcarbazole, 6 g. of acetyl chloride, and 8.5 g. of aluminum chloride in benzene (the reaction-mixture was kept for four days at room temperature) there was obtained 18 g. of an acetylation-product boiling at 350–380°/25 mm. On fractional recrystallization from a mixture of ethanol and benzene this gave:

(a) *3-Acetyl-9-benzylcarbazole* (XXVI), which formed from ethanol clumps of fine colorless needles, m.p. 112°, giving an orange-brown coloration with sulfuric acid.

Anal. Calc'd for $C_{21}H_{17}NO$: C, 84.3; H, 5.7.
Found: C, 84.2; H, 5.8.

(b) The less soluble *3,6-diacetyl-9-benzylcarbazole* (XXVII), which formed fine colorless needles m.p. 233°, giving with sulfuric acid a brownish-yellow coloration.

Anal. Calc'd for $C_{23}H_{19}NO_2$: C, 80.9; H, 5.6.

Found: C, 80.7; H, 5.6.

Both compounds underwent a Pfitzinger reaction with isatin, giving yellow cinchoninic acids, which are of interest for liver cancer research (1).

SUMMARY

1. The reactivity of several N-substituted carbazoles in Friedel-Crafts, halogenation, and nitration reactions has been investigated.

2. Several new derivatives of N-benzylcarbazole and of various N-alkylcarbazoles have been prepared for biological investigation as potential liver poisons.

PARIS V, FRANCE

REFERENCES

(1) BUU-HOÏ AND ROYER, *J. Org. Chem.*, **15**, 123 (1950).
(2) MAZZARA AND LAMBERTI-ZANARDI, *Gazz. chim. ital.*, **26** (II), 236 (1896).
(3) BUU-HOÏ AND ROYER, *Rec. trav. chim.*, **66**, 533 (1947).
(4) GRAEBE AND KNECHT, *Ann.*, **202**, 27 (1880).
(5) VOTOČEK, *Chemiker-Zeit.*, **20**, 190 (1896).
(6) LEVY, *Monatsh.*, **33**, 179 (1912).
(7) CASSELLA, German Patent 224,951, April 4, 1909.
(8) BUU-HOÏ, *Bull. soc. chim.*, [5] **11**, 578 (1944).