Nitrene. II.[1] Novel Conversion of 1-(2-Nitrobenzyl)isoquinoline Derivatives into Benz[*a*]carbazoles through Nitrene

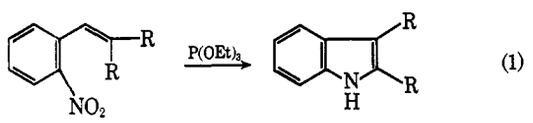
T. KAMETANI, T. YAMANAKA, AND K. OGASAWARA

Pharmaceutical Institute, School of Medicine, Tohoku University, Kitayobancho, Sendai, Japan

Received May 14, 1968

Novel conversion of 1,2-dihydro-2-methyl-1-(2-nitrobenzyl)isoquinoline (**3**) into benz[*a*]carbazole (**4**) by treatment with triethyl phosphite was established. Furthermore, 6′-nitrolaudanosine (**5**) was also converted into the corresponding dihydrobenz[*a*]carbazole derivative (**6**), but, in case of its methiodide (**7**) and 6′-nitropapaverine (**9**), benz[*a*]carbazole derivatives were not obtained.

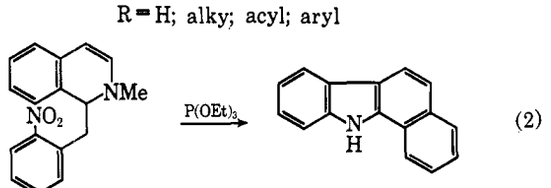
Although many investigations of the reductive cyclization of nitro compounds (**1**) to indoles (**2**) with triethyl phosphite have hitherto been carried out (eq 1),[1-8] the above-titled novel cyclization has never been investigated. We now wish to report our results which demonstrate the conversion of 1-(2-nitrobenzyl)-isoquinoline derivatives into the corresponding benz-[*a*]carbazoles by heating with an excess of triethyl phosphite under a current of nitrogen.



(1)

1 **2**

R = H; alky; acyl; aryl



(2)

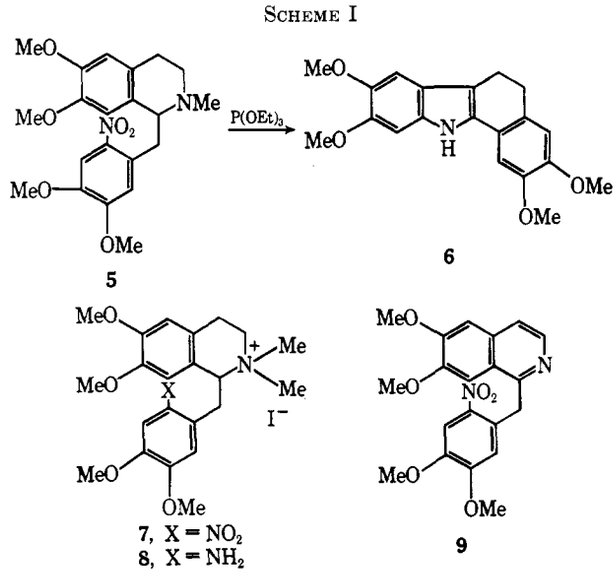
3 **4**

Treatment of the compound[9] **3** with triethyl phosphite at 160–165° gave the benz[*a*]carbazole (**4**) in 37% yield (eq 2). The product **4** was completely identical with an authentic specimen[10] from the point of the mixture melting point, ir (KBr), and nmr (in Me_2SO) spectra. Secondly, similar treatment of 6′-nitrolaudanosine (**5**)[11] with triethyl phosphite also afforded 5,6-dihydro-2,3,8,9-tetramethoxybenz[*a*]carbazole (**6**), mp 202°, in 38% yield, whose structure was elucidated from spectral data as follows; the nmr spectrum (parts per million, in $CDCl_3$) showed the C_5- and/or C_6-methylene protons at 3.08 (2 H, triplet, J = 8 cps) and 4.13 (2 H, triplet, J = 8 cps), four O-methyl protons at 3.87 (3 H), 3.90 (3 H), and 3.92 (6 H), four aromatic protons at 6.74, 6.80, 7.08, and 7.20 as singlets, respectively, and a characteristic NH proton at 6.62 as singlet, which disappeared with D_2O. Furthermore, the mass spectra of **4** and **6** showed its molecular ion peaks at *m/e* 217 (M^+) and 339 (M^+) as its base peak, respectively. The other strong ion peaks were not detected. This fact shows that both compounds **4** and **6** are stabilized owing to their conjugation.

On the other hand, application of this novel conversion into 6′-nitrolaudanosine methiodide (**7**) gave none of the expected benz[*a*]carbazole; reduction of the 6′-nitro group by triethyl phosphite occurred to give 6′-aminolaudanosine methiodide (**8**). The same treatment of 6′-nitropapaverine (**9**)[12] afforded no benz[*a*]carbazole, but an unknown compound of $C_{20}H_{18}O_5N_2$ (**10**) having two nitrogens was isolated in 4.5% yield.

These facts reveal that the unshared electron pair at the N_2 position participates in the formation of benz-[*a*]carbazole and it seems to be necessary that the 1,2-dihydro- and 1,2,3,4-tetrahydroisoquinolines should be used as starting materials for this novel conversion. In this reaction the nitrene intermediate, which would be assumed to be formed by treatment with triethyl phosphite, would attack the saturated carbon atom to give the indole derivatives, but the precise mechanism is under examination (Scheme I).

SCHEME I



5 **6**

7, X = NO_2
8, X = NH_2

9

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Experimental Section

The nmr spectra were determined on a Hitachi H-60 spectrometer with deuteriochloroform as solvent and tetramethylsilane as an internal reference. The mass spectra were obtained on a Hitachi RMU-6D mass spectrometer, using an all-glass inlet system heated to 300°. The ionizing energy was maintained at 70 eV and ionizing current at 80 μA.

Benz[a]carbazole (4).—A mixture of 1.4 g (0.005 mol) of 1,2-dihydro-2-methyl-1-(2-nitrobenzyl)isoquinoline[9] (3) and 2.5 g (0.015 mol) of triethyl phosphite was refluxed in an oil bath at 160–165° for 20 hr. After cooling, excess triethyl phosphite was removed by distillation and the residue was purified by silica gel chromatography using benzene as an eluent. Removal of the benzene fraction and recrystallization from benzene–hexane afforded 0.4 g (37%) of the benz[a]carbazole (4) as colorless needles: mp 227–228° (lit.[10] mp 228°); mass (*m/e*) 217 (M^+); ν_{max} (KBr) 3430 cm^{-1}; δ (Me_2SO) 7.10–8.65 (10 H, multiplet, aromatic protons), 12.12 ppm (1 H, singlet, NH proton, disappeared with D_2O).

Anal. Calcd for $C_{16}H_{11}N$: C, 88.45; H, 5.10; N, 6.45. Found: C, 88.62; H, 5.14; N, 6.36.

5,6-Dihydro-2,3,8,9-tetramethoxybenz[a]carbazole (6).—A mixture of 1 g (2.7 mmol) of 6′-nitrolaudanosine[11] (5) and 2.24 g (13.5 mmol) of triethyl phosphite was heated under reflux in an oil bath at 165–170° for 20 hr. After cooling the excess reagent was distilled off *in vacuo* and the residue was chromatographed on silica gel using benzene as an eluent. Evaporation of the benzene eluate and recrystallization from ethanol gave 0.35 g (38.5%) of the benz[a]carbazole derivative (6) as colorless scales: mp 202°; mass (*m/e*) 339 (M^+); ν_{max} (KBr) 3400 cm^{-1} (NH); δ ($CDCl_3$) 3.08 (2 H, triplet, J = 8 cps, C_5 or C_6 methylene protons), 3.87 (3 H, singlet, OCH_3), 3.90 (3 H, singlet, OCH_3), 3.92 (6 H, singlet, 2-OCH_3), 4.13 (2 H, triplet, J = 8 cps, C_5 or C_6 methylene protons), 6.62 (1 H, singlet, NH proton, disappeared with D_2O), 6.78, 6.80, 7.08, and 7.20 ppm (4 H, four singlets, aromatic protons).

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24, N, 4.13. Found: C, 71.00; H, 6.32; N, 4.42.

6′-Nitrolaudanosine Methiodide (7).—A mixture of 6 g of 6′-nitrolaudanosine (5), 30 ml of methanol, and 10 g of methyl iodide was heated on a water bath for 10 min, crystals of 5 being thus dissolved and then those of 7 separated in turn. After an additional 10-min heating, the crystals were collected by filtration and recrystallized from ethanol–dimethylformamide to give 7.2 g (89%) of the methiodide (7) as colorless prisms, mp 240°.

Anal. Calcd for $C_{22}H_{29}N_2O_6I$: C, 48.54; H, 5.39; N, 5.15. Found: C, 48.72; H, 5.47; N, 5.40.

6′-Aminolaudanosine Methiodide (8).—A mixture of 5.44 g (0.01 mol) of 6′-nitrolaudanosine methiodide (7) and 8.3 g (0.05 mol) of triethyl phosphite was heated under reflux in an oil bath at 160–165° for 20 hr. After removal of excess reagent, the residue was crystallized from a small amount of benzene. Recrystallization from ethanol gave 4.1 g (80.1%) of the methiodide (8) as a yellow powder: mp 231° dec; ν_{max} (KBr) 3400 cm^{-1} (NH_2 and H_2O); δ (CF_3CO_2H) 7.85, 7.50–6.60 (4 H, multiplet, aromatic protons), 4.28 (1 H, multiplet, C_1 H), 4.05, 3.99, 3.97 (12 H, three singlets, 4-OCH_3), 3.70–3.00 ppm (6 H, multiplet, C_3 H_2, C_4 H_2, and 1-benzylic proton).

Anal. Calcd for $C_{22}H_{31}N_2O_4I \cdot 0.5H_2O$: C, 50.44; H, 5.92; N, 5.16. Found: C, 50.45; H, 6.28; N, 5.58.

Reduction of 6′-Nitropapaverine[12] (9) with Triethyl Phosphite.—A mixture of 5 g of 6′-nitropapaverine (9) and 11.2 g of triethyl phosphite was heated under reflux in an oil bath at 160–165° for 20 hr. After removal of the excess of the reagent, the residue was dissolved in a small amount of ethanol, whose solution was allowed to stand to separate the crystals. Recrystallization from chloroform gave 0.2 g (4.2%) of deoxygenated product (10) as yellow prisms: mp 277–278°; mass (*m/e*) 366 (M^+) (base peak) (no characteristic patterns were observed); ν_{max} (KBr) 1618 cm^{-1}; δ ($CDCl_3$) 4.00, 4.04, 4.15 (6 H, 3 H, 3 H, three singlets), 6.99, 7.07, 7.73 (each 1 H, singlets), 7.48, 8.37 (each 1 H, doublets, J = 7 cps), 10.35 (1 H, singlet). None of these disappeared with D_2O.

Anal.[13] Calcd for $C_{20}H_{18}O_5N_2$: C, 65.56; H, 4.95; N, 7.65. Found: C, 65.67; H, 5.00; N, 7.68.

Registry No.—**4**, 239-01-0; **6**, 17953-40-1; **7**, 17953-41-2; **8**, 17953-42-3.

Acknowledgment.—We wish to express our gratitude to Miss R. Hasebe and Miss T. Yamaki for the microanalyses and Miss Y. Tadano for the nmr determinations.

(13) The structure of compound **10** could not be determined.

Reissert Compound Studies. XVIII. Analogs Derived from Chloroformates[1,2a]

FRANK D. POPP, LAWRENCE E. KATZ, CARL W. KLINOWSKI,[2b] AND JOHN M. WEFER[2c]

Department of Chemistry, Clarkson College of Technology, Potsdam, New York 13676

Received July 15, 1968

The reaction of quinoline or isoquinoline and potassium cyanide with a variety of chloroformates has given rise to the formation of the Reissert compound analogs of the types **6** and **7**. The reactions of these analogs are compared with the reactions of Reissert compounds and other Reissert compound analogs.

In connection with our studies of Reissert compounds (**1** and **2**)[3] we have previously prepared analogs of the types **3**,[4] **4**,[5] and **5**[1] from the reaction of isoquinoline and potassium cyanide with carbamoyl chlorides, sulfonyl chlorides, and chlorophosphates, respectively. The corresponding analogs could not be isolated in the quinoline series.

We now wish to report on the use of chloroformates in this reaction. Reaction of isoquinoline, potassium cyanide, and a variety of chloroformates in methylene chloride–water gave compounds of the type **6**. These compounds are included in Table I. Under these same conditions quinoline reacted to give products of the type **7** which are also included in Table I. It is of interest to note that in contrast to Reissert compounds[3,6] and Reissert compound analogs **3**–**5**[1,4,5] several of these new analogs exhibited weak absorption in the nitrile region of the infrared at 220 cm^{-1}.

Since **1** undergoes a variety of reactions such as alkylation and/or rearrangement in the presence of base,[1,6,7] **3** was unreactive in base,[4] **4** underwent elimina-

(1) Part XVII: D. M. Spatz and F. D. Popp, *J. Heterocycl. Chem.*, **5**, 497 (1968).

(2) (a) Supported in part by a Research Grant (T-329) from the American Cancer Society. Portions of this material were presented at the 1st International Congress of Heterocyclic Chemistry, Albuquerque, N. M., 1967, and the 155th National Meeting of the American Chemical Society, San Francisco, Calif., 1968. (b) National Science Foundation Undergraduate Research Participant. (c) National Institutes of Health Predoctoral Fellow.

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