[CONTRIBUTION NO. 872 FROM THE CHEMISTRY LABORATORIES OF INDIANA UNIVERSITY]

Synthesis of Tetrahydrocarbazoles and Carbazoles by the Bischler Reaction[1,2]

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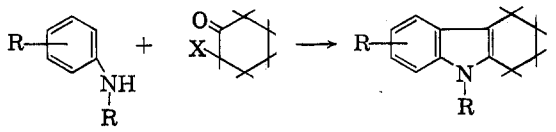
The several steps in the synthesis of carbazoles by the Bischler reaction have been studied. The reaction of 2-chlorocyclohexanone with aryl amines was best in a high boiling solvent (Cellosolve) in the presence of sodium carbonate and a small amount of quinoline or pyridine. The resulting 2-arylaminocyclohexanones could be cyclized in high yield, using a mixture of Cellosolves to attain the optimum reflux temperature, and a mixture of anhydrous magnesium chloride and the respective aryl amine as catalyst. Tetrahydrocarbazoles are susceptible to air oxidation, and accurate melting points could be obtained only on samples protected from the air. The improved preparation of a number of substituted 1,2,3,4-tetrahydrocarbazoles is reported, including the 6-phenyl and 7-methyl derivatives, which are new. These were dehydrogenated to the corresponding carbazoles, of which the 3-phenyl derivative is new, and 4-methylcarbazole has been characterized in the pure form for the first time. A color reaction, which distinguished tetrahydrocarbazoles from carbazoles or 2-arylaminocyclohexanones, is described.

The ready availability of a wide variety of aromatic amines and the ease with which 2-chlorocyclohexanone can be prepared from cyclohexanone,[3] combined with consideration of the disadvantages of the traditional synthetic methods, make the Bischler[4] synthesis a potentially attractive method for the preparation of tetrahydrocarbazoles and carbazoles.

Application of the Bischler synthesis to the preparation of tetrahydrocarbazoles was first mentioned in 1923 in a patent by Ott,[5] who claimed that α-halocyclohexanones could be condensed with primary or secondary aromatic amines to give good yields of tetrahydrocarbazoles. In the example described, 2-chlorocyclohexanone was added to



an excess of aniline at 150–160°. The yield of tetrahydrocarbazole was claimed to be nearly quantitative.

Hughes, Lions, Maunsell, and Wright[6] have reported that 6,7-dimethoxy-1,2,3,4-tetrahydrocarbazole was formed in 40% yield by the condensation of 2-chlorocyclohexanone with *p*-aminoveratrole in the presence of sodium acetate. Campbell and McCall[7] have used the Bischler reaction for the synthesis of several methyl, dimethyl, chloro and carbomethoxy derivatives of tetrahydrocarbazole in yields ranging from 13–65%.

Jones and Tomlinson[8] have reported that tetrahydrocarbazoles were formed when 2-hydroxycyclohexanone was heated with the appropriate aromatic amine in the presence of a little mineral acid. The yields reported range from 12–81% but no experimental details were given. The reaction has also been applied to aminocarbazoles.[9] Cummins and Tomlinson[10] describe the preparation of 5-methoxy-1,2,3,4-tetrahydrocarbazole by reaction of 2-hydroxycyclohexanone with 2-chloro-5-methoxyaniline followed by cyclization of the amino ketone and removal of the 8-chloro group.

The preparation of indolocarbazole derivatives by reaction of 2-chlorocyclohexanone with aminocarbazoles has been described by Plant and coworkers.[11]

Interest in the preparation of substituted carbazoles and tetrahydrocarbazoles[12] led us to study carefully the various steps involved in the application of the Bischler synthesis to the preparation of carbazoles. It was found best to prepare first pure arylaminocyclohexanones, cyclize these to the desired tetrahydrocarbazoles under carefully controlled conditions, and then dehydrogenate the purified products.

Preparation of 2-arylaminocyclohexanones. The reaction between 2-chlorocyclohexanone (I) and 2-naphthylamine (II) has been studied thoroughly with respect to the yields of 2-(2-naphthylamino)-cyclohexanone (XIII) that are obtained under

(1) This work was supported by research grant CY-1948 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) Taken from the thesis of R. D. Lake, presented in partial fulfillment of the requirements for the degree doctor of philosophy at Indiana University, September 1956.

(3) M. S. Newman, M. D. Farbman, and H. Hipsher, *Org. Syntheses*, **Coll. Vol. III,** 188 (1955).

(4) P. L. Julian, E. W. Meyer, and H. C. Printy, *Heterocyclic Compounds*, Vol. 3, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, 1952, pp. 22–35.

(5) K. Ott, German Patent **374,098**; *Chem. Abstr.*, **18**, 2175 (1924).

(6) G. K. Hughes, F. Lions, J. J. Maunsell, and L. E. A. Wright, *J. Proc. Roy. Soc. N. S. Wales*, **71**, 433 (1938).

(7) N. Campbell and E. B. McCall, *J. Chem. Soc.*, 2870 (1950).

(8) N. A. Jones and M. L. Tomlinson, *J. Chem. Soc.*, 4114 (1953).

(9) M. L. Swindells and M. L. Tomlinson, *J. Chem. Soc.*, 1135 (1956).

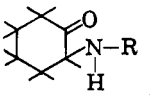
(10) J. A. Cummins and M. L. Tomlinson, *J. Chem. Soc.*, 3475 (1955).

(11) J. A. Hall and S. G. P. Plant, *J. Chem. Soc.*, 116 (1953); P. H. Carter, A. R. Katritzky, and S. G. Plant, *J. Chem. Soc.*, 337 (1955).

(12) E. Campaigne, L. Ergener, J. V. Hallum, and R. D. Lake, *J. Org. Chem.*, **24**, 487 (1959).

TABLE I

2-ARYLAMINOCYCLOHEXANONES



No.	R	Yield, %	M.P., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
III	C_6H_5	60	84.5–85	76.15	75.66	7.99	7.93	7.40	7.66
IV	o-$CH_3C_6H_4$	33	47–48	76.80	77.24	8.43	8.48	6.89	6.97
V	m-$CH_3C_6H_4$	50	70.5–71	76.80	76.58	8.43	8.07	6.89	7.11
VI	p-$CH_3C_6H_4$	65	112–113	76.80	77.08	8.43	8.41	6.89	7.08
VII	p-$CH_3OC_6H_4$	63	100.5–101.5	71.36	71.58	7.83	7.71	6.40	6.65
VIII	p-$C_6H_5C_6H_4$	64	125.5–126	81.47	81.39	7.22	7.22	5.28	5.54
IX	p-ClC_6H_4	57	132–133[a]	64.42	64.71	6.31	6.23	6.26	6.51
X	p-BrC_6H_4	58	141–142[b]	53.74	54.19	5.26	4.92	5.22	5.46
XI	2-Cl-5-$CH_3C_6H_3$	38	79–80	65.68	65.38	6.78	6.61	5.89	6.24[c]
XII	1-$C_{10}H_7$	51	103.5–104.5	80.30	80.20	7.16	7.10	5.85	5.90
XIII	2-$C_{10}H_7$	45	145–146	80.30	80.87	7.16	7.21	5.85	5.93

[a] Campbell and McCall,[7] reported m.p. 132–134°. [b] Reported[3] m.p. 143–144°. [c] Calcd.: Cl, 14.91. Found: Cl, 14.93.

different reaction conditions. Equimolar amounts of I and II (or a slight excess of I) were allowed to react at the boiling point of the solvent, in the presence of an excess of anhydrous sodium carbonate, until the evolution of carbon dioxide had ceased. When sodium carbonate and 2-naphthylamine were the only bases present, 5,6,7,8-tetrahydro-3,4-benzocarbazole (XIV) was formed as a by-product. Addition of a small amount of pyridine or quinoline appeared to eliminate cyclization as a competing reaction and also lessened contamination of the product with colored materials. When the sodium carbonate was omitted (1.1 equiv. of pyridine present) the only product was XIV.

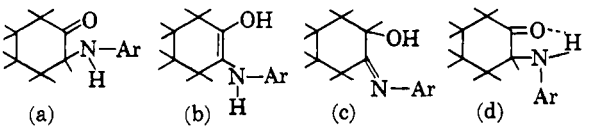
The reaction was very sluggish in dioxane and did not proceed at all in tetrahydrofuran. With dimethylformamide as solvent only a small amount of XIV could be isolated. The use of *n*-propanol in place of ethanol increased the yield of XIII from 32–45%. Higher boiling solvents such as *n*-butanol or cellosolve increased the rate of reaction but failed to bring about any further improvement in yield.

The presence of an excess of II, portionwise addition of II or dropwise addition of I all had a detrimental effect on the yield. Addition of 0.1 equiv. of potassium iodide or replacement of I by 2-bromocyclohexanone also decreased the yield of XIII.

All the remaining 2-arylaminocyclohexanones listed in Table I were prepared by a procedure very similar to that found best for XIII. Equivalent quantities of I and aromatic amine were allowed to react in boiling methylcellosolve, in the presence of 0.1 equiv. of quinoline and an excess of anhydrous powdered sodium carbonate.

All the arylamino ketones having *para*-substituents were quite stable but the others tended to deteriorate upon standing, apparently due to oxidation.

The assumption has been made that the 2-arylaminocyclohexanones exist in the form indicated by the formula (a) rather than in other possible enol forms such as (b) or (c). The infrared



spectra of several representative compounds of this series (Table II) show quite conclusively that this assumption is correct, at least for the solid state. The NH and CO stretching frequencies fall within normal limits.[13] There was no other absorption which could be attributed to the presence of either hydroxyl or imino groups. The sharpness of the NH bands and the closeness of the carbonyl absorption to that of cyclohexanone itself (1710 cm.$^{-1}$)[13] indicates that hydrogen bonding such as that indicated in formula (d) is probably weak.

TABLE II

NH AND CO INFRARED ABSORPTION BANDS OF 2-ARYLAMINOCYCLOHEXANONES

Substituent	Wave Number, Cm.$^{-1}$ NH	CO
2-$C_{10}H_7NH$	3370	1705
p-$CH_3C_6H_4NH$	3320	1702
o-$CH_3C_6H_4NH$	3420	1715
p-ClC_6H_4NH	3400	1710
$C_6H_5NC_2H_5$	..	1722

Chlorination of 4-methylcyclohexanone, by the same procedure as that used for preparation of I, gave, as expected, two stereoisomeric chloro ketones, which appeared to be interconverted

(13) L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York, 1954.

TABLE III

CYCLIZATION OF 2-ANILINOCYCLOHEXANONE

Exp.	Catalyst	Solvent	Temp., °C.	Time Hr.	Yield, %
A	$ZnCl_2$	C_2H_5OH	78	12.0	0
B	$ZnCl_2$	$CH_3OC_2H_4OH$	125	12.0	15
C	$ZnCl_2$	n-$C_4H_9OC_2H_4OH$	171	1.0	0
D	$ZnCl_2$	$(CH_3)_2NCHO$	153	12.0	7
E	$ZnCl_2$	CH_3CO_2H	118	12.0	0
F	$(CH_2)_5NH\cdot HCl$[a]	C_2H_5OH	78	6.0	0[b]
G	NH_4Br	Cellosolves[c]	130	4.0	48
H	H_3PO_4	Cellosolves[c]	130	4.0	33
I	CH_3CO_2H	CH_3CO_2H	118	18.0	15
J	$CH_3CO_2H/C_6H_5NH_2$	CH_3CO_2H	118	12.0	74
K	$MgCl_2/C_6H_5NH_2$	CH_3CO_2H	118	12.0	80
L	$C_6H_5NH_2\cdot HCl$	Cellosolves[c]	130	4.0	89
M	$MgCl_2/C_6H_5NH_2$	Cellosolves[c]	130	4.0	88
N	$MgCl_2$	Cellosolves[c]	130	4.0	60
O	$MgCl_2$	C_2H_5OH	78	4.0	0
P	$MgCl_2$	n-C_3H_7OH	97	4.0	18
Q	$MgCl_2$	$CH_3OC_2H_4OH$	125	4.0	30

[a] Piperidine hydrochloride. [b] 80% of IX recovered. [c] 3:2 Mixture of methyl and butylcellosolves.

upon standing. Godchot and Bedos[14] have reported similar results. Only one product was obtained from the reaction of either isomer with II. That no rearrangement had taken place is indicated by the fact that ring closure gave the expected 7-methyl-5,6,7,8-tetrahydro-3,4-benzocarbazole.[12] This amino ketone is therefore undoubtedly 4-methyl-2-(2-naphthylamino)cyclohexanone. Reaction of aniline with 2-chloro-4-methylcyclohexanone gave a mixture of isomeric anilino ketones, only one of which was isolated in pure form. These were probably stereoisomers but the possibility that partial rearrangement had occurred and that the product isolated was actually 2-anilino-5-methylcyclohexanone cannot be rigorously excluded. No clue was provided by the result of ring closure, since a mixture of 2- and 3-methyl-1,2,3,4-tetrahydrocarbazoles was obtained. Such rearrangements of arylaminoketone, occurring under ring-closure conditions, are well known.[4]

Preparation of tetrahydrocarbazoles. Both α- and β-naphthylaminocyclohexanones were cyclized in good yield by boiling absolute ethanolic zinc chloride to 5,6,7,8-tetrahydro-1,2-benzocarbazole (XV) or 5,6,7,8-tetrahydro-3,4-benzocarbazole (XIV), respectively. However, attempted extension of the alcoholic zinc chloride method of ring closure to the case of 2-anilinocyclohexanone (III) gave only an intractable oil. As indicated in Table III (Experiment B), zinc chloride in methylcellosolve gave a small amount of 1,2,3,4-tetrahydrocarbazole (XVI) but at the higher temperature provided by butylcellosolve, no XVI could be isolated. It was apparent that the amino ketone was largely destroyed under these conditions. In this connection it is to be noted that zinc chloride in acetic acid gave no tetrahydrocarbazole, but acetic acid alone afforded a small yield of XVI.

Phosphoric acid, ammonium bromide, or anhydrous magnesium chloride in a mixture of methyl and butylcellosolves gave XVI in yields of 33, 48, and 60%, respectively. The catalytic effect of aromatic amines was clearly demonstrated by the fact that a combination of magnesium chloride and aniline afforded XVI in 88% yield (*cf.* Table III. Experiments M, N). This result was expected on the basis of the reaction mechanism proposed by Bischler[15] involving formation of an ene-diamine by reaction of the aromatic amine with the amino ketone, which then undergoes ring closure.

The magnesium chloride–amine catalyst proved to be quite satisfactory for the preparation of the methyl tetrahydrocarbazoles (XVII, XIX), 6-methoxy-1,2,3,4-tetrahydrocarbazole (XXI), and 9-ethyl-1,2,3,4-tetrahydrocarbazole (XXVI) (see Table IV). Equimolar quantities of arylamino cyclohexanone and the corresponding amine and two molar equivalents of anhydrous magnesium chloride were refluxed under nitrogen for 4 hr. in a 3:2 mixture of methyl and butylcellosolve. The crude tetrahydrocarbazoles were pure enough to give very high yields of the corresponding carbazoles. 2-(*p*-Biphenylamino) cyclohexanone (VIII) was somewhat more difficult to cyclize and required a higher reaction temperature.

The cyclization of 2-(*m*-toluidino)cyclohexanone (V) gave a mixture of 7-(XVIII) and 5-methyl-1,2,3,4-tetrahydrocarbazole (XX) in a ratio of about three to one. Although others workers[7,16] have reported an inability to isolate pure compounds from this mixture of isomers, it was found that

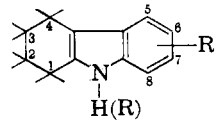
(14) M. Godchot and P. Bedos, *Compt. rend.*, **180**, 295 (1925).

(15) A. Bischler and H. Brion, *Ber.*, **25**, 2860 (1892).

(16) M. W. G. Coldham, J. W. Lewis, and S. G. P. Plant, *J. Chem. Soc.*, 4528 (1954).

TABLE IV

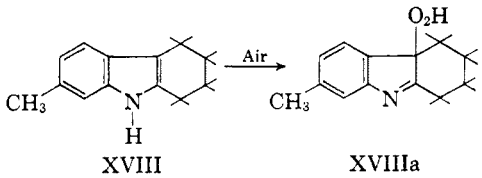
TETRAHYDROCARBAZOLES



No.	R	Yield, %	Found, *in Vacuo*	M.P., °C., Found *in Air*	Reported	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
XVI	H	88	118.5–119.5	113–118	115–116[a]	84.17	83.81	7.65	7.68	8.18	8.31
XVII	8-CH_3	97	97–98	93–96	97–98[d]	84.28	84.54	8.16	8.10	7.56	7.57
XVIII	7-CH_3	95[e]	148–149	126–138		84.28	84.59	8.16	8.16	7.56	7.63
XIX	6-CH_3	95	145–146	130–142	141–142[d]	84.28	84.42	8.16	8.11	7.56	7.57
XX	5-CH_3	68[f]	150–150.5	140–147	140–147[g]	84.28	84.39	8.16	8.13	7.56	7.55
XXI	6-CH_3O	92	107.5–108.5	92–103	93–105[h]	77.58	77.36	7.51	7.40	6.96	7.16
XXII	6-C_6H_5	63[i]	153–154	149–152		87.41	87.43	6.93	6.82	5.66	5.88
XXIII	6-Cl	90	146–147	143–145	141–143[j]	70.07	69.93	5.88	5.88	6.81	6.94[k]
XXIV	6-Br	60	151.5–152	148.5–150	153[l]	57.62	57.72	4.84	4.77	5.60	5.79[m]
XXV	5-CH_3-8-Cl	70	69–70	67–68.5	64.5[n]	71.06	71.19	6.42	6.44	6.38	6.46[o]
XXVI	9-C_2H_5	61	oil[b,c]			84.37	84.41	8.60	8.70	7.03	6.96

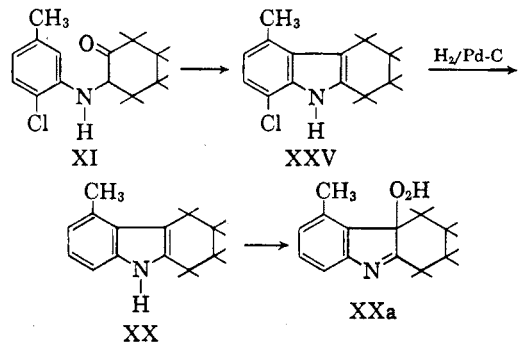
[a] C. U. Rogers and B. B. Corson, *Org. Syntheses*, **30**, 90 (1950). [b] B.p. 105–106° (0.1 mm.), n_D^{25} 1.5912. [c] Adkins and Coonradt[27] report n_D^{25} 1.5498. [d] B. Barclay and N. Campbell, *J. Chem. Soc.*, 530 (1945). [e] Mixture of 5- and 7-methyl isomers. [f] Over-all yield, based on 2-(2-chloro-5-methylanilino) cyclohexanone. [g] Ref. 10. [h] Ref. 20. [i] As the picrate. [j] Ref. 6. [k] Calcd: Cl, 17.24. Found: Cl, 17.29. [l] Ref. 24. [m] Calcd: Br, 31.95. Found: Br, 31.77. [n] K. H. Pausacker and R. Robinson, *J. Chem. Soc.*, 1557 (1947). [o] Calcd: Cl, 16.14. Found: Cl, 16.29.

XVIII could be easily obtained by crystallization. All attempts to separate XX by fractional crystallization or chromatography were unsuccessful. The purity of XVIII was demonstrated by quantitative dehydrogenation to 2-methylcarbazole, which melted sharply without purification. Upon standing exposed to the air in petroleum ether solution, XVIII underwent rapid oxidation to form 11-hydroperoxy-7-methyl-1,2,3,4-tetrahydrocarbazolenine (XVIIIa) which was characterized by elemental analysis, infrared spectrum, solubility in acid, and its ability to oxidize iodide ion.



XVIII XVIIIa

Coldham, Lewis, and Plant[16] have described the synthesis of XX, m.p. 140–146°, from 2-hydrazino-4-methylbenzoic acid and cyclohexanone, followed by decarboxylation. Cummins and Tomlinson[10] have reported the synthesis of a compound, also presumably XX, by hydrogenolysis of 1-chloro-4-methyl-5,6,7,8-tetrahydrocarbazole, but neither product was well characterized. It was therefore considered advisable to synthesize XX in order to characterize it more thoroughly. This was accomplished by cyclization of the amino ketone (XI) and hydrogenolytic removal of the chlorine atom of XXV, a method patterned after that of Cummins and Tomlinson.[10] XX was characterized by its hydroperoxide, picrate, and by dehydrogenation to 4-methylcarbazole.

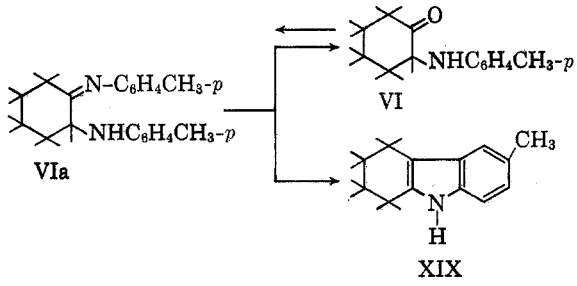


XI XXV XX XXa

All attempts to cyclize 2-(*p*-bromoanilino) cyclohexanone (X) with magnesium chloride and *p*-bromoaniline gave only tars. Magnesium chloride and aniline, however, gave a small yield of 1,2,3,4-tetrahydrocarbazole (isolated as the picrate), a result which parallels that of Campbell and McCall.[3] Cyclization of X took place satisfactorily in the presence of *p*-bromoaniline and *p*-bromoaniline sulfate, giving 6-bromo-1,2,3,4-tetrahydrocarbazole (XXIV) in 60% yield. A 90% yield of the 6-chloro-analog (XXIII) was obtained under similar conditions. The difference in reactivity of the chloro- and bromoanilinocyclohexanones was even more evident in the results of Campbell and McCall[7] who reported that *p*-chloroaniline hydrochloride gave XXIII in 22% yield but the *p*-bromo analog was not cyclized under these conditions.

2-*p*-Toluidinocyclohexanone reacted with *p*-toluidine in the presence of zinc chloride to form a compound, $C_{20}H_{24}N_2Cl_2Zn$, believed to be the zinc complex of the diamine (VIa). The free diamine was very unstable but could be hydrolyzed to the parent amino ketone (VI) or cyclized to 6-methyl-

1,2,3,4-tetrahydrocarbazole (XIX). These results are in keeping with the observations of Julian *et al.*[17]



Ring closure of 2-anilino-4-methylcyclohexanone catalyzed by aniline and magnesium chloride led to a mixture of 2- and 3-methyl-1,2,3,4-tetrahydrocarbazoles in good yield. This behavior is like that of 2-anilino-5-methylcyclohexanone, observed by Campbell and McCall.[7] There is a remarkable similarity in the melting points of the two mixtures (78–81° and 77–82°) suggesting that either isomeric amino ketone gives a mixture of the same composition. No conditions could be found under which 2-anilino-4-methylcyclohexanone could be cyclized with formation of only one of the isomeric methyl tetrahydrocarbazoles. On the other hand, the behavior of 2-anilino-4-methylcyclohexanone is in contrast to that of the 2-naphthylamino ketone[12] which gave only one product, a fact which serves further to emphasize the possible fundamental difference between the zinc chloride catalyzed ring closures and those affected by acids in the presence of aromatic amine catalysts.

A few experiments were conducted to test the feasibility of omitting the isolation of the arylaminocyclohexanones. This abbreviated procedure, described in the experimental part, generally gave higher yields, but the tetrahydrocarbazoles so obtained were less pure than those obtained by the two step procedure.

The greater portion of the work with tetrahydrocarbazoles was hindered by the persistent tendency of these compounds to melt over a wide range. This behavior was exhibited by all the tetrahydrocarbazoles studied except the benzo derivatives, but was most pronounced with those having methyl or methoxy substituents (see Table IV). These materials commonly melted higher and more sharply before crystallization than afterward, even though the physical appearance was improved. The melts were invariably yellow. A freshly prepared sample of XVI melted at 117–118°, 113–118° two weeks later, and 111–117° after 16 months, even though there was no visible signs of deterioration. Although Freudenberg has stated[18] that tetrahydrocarbazole is perfectly stable, other writers have commented[19,20] on the wide melting ranges found for apparently pure compounds of this type.

It was found that the melting points of the tetrahydrocarbazoles were higher and much sharper when taken in evacuated capillaries (see Table IV), and the melts were clear and colorless. It is well known that tetrahydrocarbazoles absorb oxygen from the air to form hydroperoxides,[21] especially in inert solvents. Probably the broad melting ranges found after recrystallization are due to traces of hydroperoxides, and formation of hydroperoxides during melting in air tends to depress the melting points of pure tetrahydrocarbazoles. It is therefore recommended that pure samples of tetrahydrocarbazoles be stored in an inert atmosphere, and melting points also be taken in the absence of oxygen.

It was discovered that when a glacial acetic acid solution of any of the tetrahydrocarbazoles studied was treated with bromine, allowed to stand for a few minutes, and then warmed on the steam bath, a green or blue coloration developed. The only exception was 9-ethyl-1,2,3,4-tetrahydrocarbazole for which the test failed. Most tetrahydrocarbazoles not having a substituent on the nitrogen atom gave a very intense color, while those having an *N*-methyl group generally gave comparatively weak colors. The hydroperoxides of 7- or 5-methyl-1,2,3,4-tetrahydrocarbazole also gave a positive test as did indole and pyrrole but the arylamino cyclohexanones and carbazoles failed to give a color reaction. The test was therefore useful in following the success of ring-closure reactions.

Color formation appeared to be catalyzed by acid. No color was formed in acetic acid in the presence of sodium acetate or pyridine, although a considerable quantity of bromine was consumed. The color reaction took place to only a very slight extent or not at all in carbon tetrachloride, but when acetic acid was added the characteristic coloration appeared almost immediately and darkened as the concentration of acetic acid was increased. Addition of a small amount of *p*-toluenesulfonic acid had an even more pronounced effect. The colors were destroyed by a large excess of bromine or chlorine or by small amounts of bases such as sodium acetate or pyridine.

Preparation of carbazoles. Dehydrogenation of the tetrahydrocarbazoles was in most cases easily accomplished by refluxing in xylene in the presence of a 30% palladium on charcoal catalyst. If reasonable precautions were exercised to prevent poisoning of the catalyst, the simple carbazoles were isolated in excellent yield and in a high state of purity

(17) P. Julian, E. Meyer, A. Magnani, and W. Cole, *J. Am. Chem., Soc.*, **67**, 1203 (1945).

(18) W. Freudenberg, in R. C. Elderfield's *Heterocyclic Compounds*, Vol. 3, John Wiley Sons, Inc. New York, 1952, p. 295.

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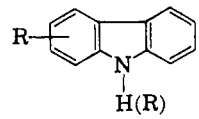
TABLE V

CARBAZOLES



No.	R	Yield, %	M.P., °C. Found	M.P., °C. Reported	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
XXVII	H	91	246–246.5	245[a]						
XXVIII	1-CH_3	95	120.5–121	120.5[b]	86.15	86.21	6.12	6.14	7.73	7.73
XXIX	2-CH_3	99[g]	261–262	259[c]	86.15	85.91	6.12	6.04	7.73	7.89
XXX	3-CH_3	86	206.5–207.5	207[d]	86.15	86.28	6.12	6.06	7.73	7.89
XXXI	4-CH_3	89	129.5–130	115–116[e]	86.15	86.09	6.12	6.09	7.73	7.83
XXXII	3-CH_3O	89	150.5–151	151–152[f]	79.16	79.06	5.62	5.63	7.10	7.06
XXXIII	3-C_6H_5	60	220.5–221.5		88.86	88.33	5.39	5.40	5.76	5.83
XXXIV	9-C_2H_5	79	70–70.5	70[h]	86.12	85.96	6.71	6.68	7.17	7.01

[a] S. H. Tucker, *J. Chem. Soc.*, 546 (1926). [b] F. Ullmann, *Ann.*, *332*, 82 (1904). [c] N. Campbell and B. Barclay, *J. Chem. Soc.*, 530 (1945). [d] S. G. P. Plant and S. H. Oakeshott, *J. Chem. Soc.* 1212 (1926). [e] K. H. Pausacker and R. Robinson, *J. Chem. Soc.*, 1557 (1947). [f] A. H. Milne and M. L. Tomlinson, *J. Chem. Soc.*, 2789 (1952). [g] Yield based on pure 7-methyltetrahydrocarbazole. When a mixture of the 5- and 7-methyl isomers was used, the yield was 74%. [h] F. R. Storrie and S. H. Tucker, *J. Chem. Soc.*, 2255 (1931).

TABLE VI

DERIVATIVES OF TETRAHYDROCARBAZOLES AND CARBAZOLES

No.	Deriv. Type[a] (Color)[b]	M.P., °C.	Empirical Formula	Nitrogen, % Calcd.	Nitrogen, % Found
XVI	P (r.)	146–147[c]	$C_{18}H_{16}N_4O_7$	14.00	14.24
XVII	P (br.)	132–133[d]	$C_{19}H_{18}N_4O_7$	13.52	13.40
XVIII	P (br.)	143.5–144.5	$C_{19}H_{18}N_4O_7$	13.52	13.35
XIX	P (br.)	150–151[e]	$C_{19}H_{18}N_4O_7$	13.52	13.51
XX	P (br.)	155–155.5	$C_{19}H_{18}N_4O_7$	13.52	13.62
XXI	P (r.)	136–137	$C_{19}H_{18}N_4O_8$	13.02	12.88
XXII	P (br.)	152–153	$C_{24}H_{20}N_4O_7$	11.76	11.44[f]
XXIII	T (r.)	184–186	$C_{18}H_{15}ClN_4O_6$	13.38	13.35
XXIV	T (r.)	186–187	$C_{18}H_{15}BrN_4O_6$	12.10	12.28
XXV	P (br.)	151.5–152	$C_{19}H_{17}ClN_4O_7$	12.49	12.49
XXVI	T (r.)	127.5–128.5	$C_{20}H_{20}N_4O_6$	13.59	13.64
XXVIII	T (o.)	165–165.5	$C_{19}H_{14}N_4O_6$	14.21	14.28
XXIX	T (o.)[g]	176–176.5	$C_{19}H_{14}N_4O_6$	14.21	14.50
XXX	P (r.)	181–182[h]	$C_{19}H_{14}N_4O_7$	13.66	13.44
XXXI	P (r.)	168–169[i]	$C_{19}H_{14}N_4O_7$	13.66	13.86
XXXII	T (r.)	158–158.5	$C_{25}H_{17}N_7O_{13}$[j]	15.73	15.70
XXXIII	T (o.)	154.5–155.5	$C_{30}H_{19}N_7O_{12}$[j]	14.65	14.50
XXXIV	P (r.)	104–104.5	$C_{20}H_{16}N_4O_7$	13.21	13.32

[a] T = 1,3,5-trinitrobenzene addition compound, P = Picrate. [b] r. = red, br. = brown, o. = orange. [c] W. H. Perkin and S. G. P. Plant, *J. Chem. Soc.*, 119, 1831 (1921), give m.p. 147°. [d] Campbell and Barclay, *J. Chem. Soc.*, 530 (1945), give m.p. 131–133°. [e] K. H. Pausacker and C. I. Shubert, *J. Chem. Soc.*, 532 (1945), give m.p. 149°. [f] Calcd: C, 60.50; H, 4.23. Found: C, 60.72; H, 4.45. [g] Picrate, orange needles, m.p. 169–170°, dec. on attempted purification. W. Borsche, A. Witte, and W. Bothe[19] reported: red needles, m.p. 167°. [h] Campbell and Barclay, *J. Chem. Soc.*, 530 (1945) reported m.p. 179–181°. [i] Pausacker and Robinson, *J. Chem. Soc.*, 1557 (1947) reported m.p. 160.5°. [j] Corresponds to two molecules of trinitrobenzene and one of the carbazole per molecule of complex.

merely by removal of the catalyst and evaporation of the solvent. The benzo derivatives, particularly 5,6,7,8-tetrahydro-1,2-benzocarbazole, underwent dehydrogenation with somewhat greater difficulty, but if the catalyst was sufficiently active these, too, were aromatized in satisfactory yield.

EXPERIMENTAL[22]

Materials. Aromatic amines were commercial materials, with the exception of *p*-aminobiphenyl and *p*-chloroaniline, purified by crystallization or distillation. 2-Chlorocyclohexanone (I) was prepared by the method of Newman, Farbman, and Hipsher.[3] Methylcellosolve was fractionated through an efficient column. Cellosolve and butylcellosolve were refluxed with *p*-toluidine prior to distillation. Magnesium chloride was a commercial anhydrous grade supplied by Dow Chemical Co. Palladium on charcoal catalyst was obtained from American Platinum Works and was carefully

(22) Microanalyses by Miss J. Dickey. Melting points are corrected and boiling points uncorrected. Melting points, *in vacuo*, were obtained by sealing the sample in a capillary at 4–5 mm. pressure. At lower pressures sublimation was troublesome.

protected from the laboratory atmosphere in order to maintain the high activity necessary for dehydrogenations.

2-Chloro-4-methylcyclohexanone was prepared by a procedure similar to that used for I. To a vigorously stirred mixture of 336 g. (3.00 moles) of 4-methylcyclohexanone (Eastman Kodak Co., redistilled) and 900 ml. of water was added during 1.25 hr. 215 g. (3.0 moles) of chlorine. The temperature was maintained at 35–45° by cooling in an ice bath. The organic layer was separated and the aqueous layer extracted with three 150-ml. portions of ether. The combined ether extracts were then washed with 150 ml. of water and 150 ml. of saturated sodium chloride solution. After drying over sodium sulfate and removal of the ether, the residue was distilled through a short Vigreux column, 387 g. of distillate (boiling range 55–100°/4 mm.) being collected. The crude product was then fractionated through a 60 × 1.5 cm. column packed with $^3/_{16}$-in. glass helices. After a forerun of 77.8 g., there was obtained 60.3 g. (14%) of a *low boiling isomer*, (b.p. 76–77°/10 mm.) n_D^{18} 1.4720. (Godchot and Bedos[14] reported: b.p. 80–82°/12 mm., n_D^{18} 1.4705, d^{18} 1.0994).

After an intermediate fraction of 25.3 g., boiling range 77–108°/10 mm. (presumably a mixture of isomers) 195.3 g. (44%) of the *high boiling isomer*, b.p. 109–110°/10 mm., n_D^{18} 1.4798, was collected. (Godchot and Bedos[14] reported a high boiling isomer, b.p. 110–112°/12 mm., n_D^{18} 1.4649, d^{18} 1.0749).

After having stood for several months, 134 g. of the high boiling isomer was refractionated, giving 35.0 g. of a low boiling liquid, b.p. 75.0–75.6°/10 mm., n_D^{25} 1.4682–1.4683. A constant boiling middle cut had the following physical constants: n_D^{25} 1.4683, d_{25}^{25} 1.0992, I.R. 1730 cm.$^{-1}$ (CCl_4). After standing at room temperature for 40 hr., the refractive index was 1.4712.

Anal. Calcd. for $C_7H_{11}ClO$: C, 57.34; H, 7.56; Cl, 24.18. Found: C, 56.93; H, 7.52; Cl, 24.19.

After an intermediate fraction of 51.5 g. (n_D^{25} 1.4683–1.4757) 18.2 g. of a high boiling fraction, b.p. 104–104.5°/10 mm., n_D^{25} 1.4757–1.4762, was collected. A middle cut, n_D^{25} 1.4757, d_{25}^{25} 1.1225, I.R. 1740 ,1730 cm.$^{-1}$ (CCl_4), gave a high value for chlorine, apparently due to contamination with polychlorinated by-products. After 40 hr. the refractive index had increased to 1.4770.

Anal. Calcd. for $C_7H_{11}ClO$: C, 57.34; H, 7.56; Cl, 24.18. Found: C, 57.29; H, 7.17; Cl, 25.52.

2-Anilino-4-methylcyclohexanone. A mixture consisting of 9.3 g. (0.10 mole) of aniline, 14.7 g. (0.10 mole) of 2-chloro-4-methylcyclohexanone, 1.3 g. (0.010 mole) of quinoline, 21 g. (0.20 mole) of sodium carbonate and 75 ml. of methylcellosolve was heated under reflux for 0.75 hr. Filtration of the cooled reaction mixture and removal of solvent *in vacuo*, followed by careful crystallization of the residual oil from aqueous methanol provided 8.9 g. (44%) of colorless crystals, m.p. 62–70.5°. Four crystallizations from petroleum ether (b.p. 30–60°) gave colorless prisms, m.p. 73–74°. The crude product was presumably a mixture of isomers, since a sample which had been crystallized two times and melted at 61–72° gave a satisfactory analysis.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 76.80; H, 8.43; N, 6.89. Found: C, 77.13; H, 8.50; N, 7.06.

2-(2-Naphthylamino)cyclohexanone (XIII). (A) *Ethanol solvent.* A mixture of 66.4 g. (0.500 mole) of 2-chlorocyclohexanone (I), 86.0 g. (0.600 mole) of 2-naphthylamine (II), 53 g. (0.50 mole) anhydrous sodium carbonate, and 250 ml. of absolute ethanol was refluxed, with stirring, for 7 hr. and the hot reaction mixture filtered. The product separated from the filtrate after cooling in the refrigerator overnight and was filtered and washed with cold methanol, to give 59.0 g. of pink crystals, m.p. 105–133°. Two crystallizations from *n*-propanol gave 10.0 g. (8%) of pale yellow needles of XIII, m.p. 145–146°.

Dilution of the filtrates from the crystallization of XIII with an equal volume of methanol and cooling in the refrigerator produced 12.3 g. (11%) of 5,6,7,8-tetrahydro-3,4-benzocarbazole (XIV), m.p. 135–138°, undepressed by admixture with an authentic sample.

(B) *Ethanol solvent, pyridine added.* Experiment (A) was repeated on a one-fifth scale with the addition of 1.6 g. (0.02 mole) of pyridine. Crystallization of the crude product from absolute ethanol gave 7.6 g. (32%) of XIII, m.p. 141–144°. Dilution of the filtrate with hexane failed to produce any precipitate.

(C) *Cellosolve solvent.* Repetition of Experiment (B) using Cellosolve as the solvent gave, after a reflux period of 0.5 hr., a 43% yield of XIII. Similar results were obtained using *n*-propanol or *n*-butanol solvents. Other variations in the procedure, such as adding I or II portionwise or using 2-bromocyclohexanone in place of I, had a detrimental effect on the yield.

2-p-Chloroanilinocyclohexanone (IX). A mixture of 38.3 g. (0.300 mole) of *p*-chloroaniline, 39.9 g. (0.300 mole) of I, 3.9 g. (0.030 mole) of quinoline, 48 g. (0.45 mole) of sodium carbonate, and 250 ml. of methylcellosolve was refluxed for 0.75 hr. The hot reaction mixture was quickly filtered and the filter cake washed with three 35-ml. portions of hot methanol. After standing in the refrigerator overnight the mixture was filtered and washed with cold methanol, giving 39.3 g. of crude product, m.p. 129–132.5°. Reduction of the volume of the filtrate to about 100 ml. provided a second crop of 4.1 g., m.p. 127.5–132°. Crystallization of the combined crops from absolute ethanol gave 37.9 g. (57%) of IX as colorless prisms, m.p. 131.5–133°.[7]

2-p-Bromoanilinocyclohexanone (X), *2-p-biphenylylaminocyclohexanone* (VIII), and *2-p-toluidinocyclohexanone* (VI) were prepared in a similar manner. For *2-p-anisidinocyclohexanone* (VII) it was necessary to remove the methylcellosolve and dilute the oily residue with methanol in order to induce crystallization.

2-Anilinocyclohexanone (III). A mixture of 26.6 g. (0.200 mole) of I, 18.6 g. (0.200 mole) of aniline, 2.6 g. (0.020 mole) of quinoline, 30 g. (0.3 mole) of sodium carbonate, and 150 ml. of methylcellosolve was refluxed, with stirring, for 45 min. The cooled reaction mixture was then filtered and the inorganic residue washed with methanol. The solvent was removed *in vacuo* and the oily residue taken up in 60 ml. of chloroform. A little Celite was added and the mixture filtered and washed with two 10-ml. portions of hot chloroform. Removal of the chloroform at reduced pressure, followed by cooling and addition of 80 ml. of hexane caused precipitation of the amino ketone. After cooling in an ice bath for 1 hr., the mixture was filtered and washed with hexane. The yield was 22.7 g. (60%) of light yellow crystals, m.p. 83–84°. Decolorization with Norit and crystallization from a methanol and water mixture provided 17.9 g. of colorless leaves, m.p. 83.5–84.5°.

2-(1-Naphthylamino)cyclohexanone (XII) and *2-m-toluidinocyclohexanone* (V) were prepared in a similar manner. For *2-o-toluidinocyclohexanone* (IV) the work-up was modified as follows: The combined filtrate and washings were distilled through a short Vigreux column, the fraction distilling at 122–127° (0.2 mm.) being collected. The amino ketone crystallized upon cooling and trituration with hexane.

2(N-Ethylanilino)cyclohexanone was prepared in the same way as III, the crude product being obtained in 42% yield as an oil, b.p. 127–128° (0.05 mm.). A solution of 2.00 g. of the crude oil in 90 ml. of hexane was passed through a 75 × 1.6 cm. alumina column. Elution with 180 ml. of 2:1 hexane-benzene and removal of solvent *in vacuo*, produced 0.14 g. of a colorless oil, the infrared spectrum of which was identical to that of 9-ethyl-1,2,3,4-tetrahydrocarbazole.

Elution with 450 ml. of benzene gave 1.53 g. of 2-*N*-ethylanilinocyclohexanone as an amber oil which darkened upon standing, n_D^{25} 1.5607. The infrared spectrum had strong absorption in the carbonyl stretching region (1722 cm.$^{-1}$).

Anal. Calcd. for $C_{14}H_{19}NO$: N, 6.45. Found: N, 6.46.

2-(2-Chloro-5-methylanilino)cyclohexanone (XI). 3-Nitro-

4-aminotoluene[23] was diazotized and converted to the chloro derivative *via* the Gatterman reaction. 3-Nitro-4-chlorotoluene was thus obtained as a pale yellow liquid, b.p. 78–79°[24] (0.4 mm.) m.p. 7°, n_D^{25} 1.5557. Reduction with iron and dilute hydrochloric acid followed by steam distillation gave 3-amino-4-chlorotoluene m.p. 31–32° (previously reported[24] to melt at 29–30°). Reaction with 2-chlorocyclohexanone, by the procedure described above for III, gave, after crystallization from petroleum ether (b.p. 30–60°), XI, m.p. 79–79.5° (38% yield).

Reaction of 2-p-toluidinocyclohexanone (VI) *with p-toluidine and zinc chloride.* Ten g. (0.05 mole) of VI, 5.3 g. (0.05 mole) of *p*-toluidine, 13.4 g. (0.1 mole) of anhydrous zinc chloride, and 250 ml. of absolute ethanol were refluxed under nitrogen for 4 hr. Cooling in an ice bath, filtration, and washing with ethanol gave 17.4 g. (82%) of nearly colorless prisms melting with decomposition at 248°, which were insoluble in most organic solvents, but very soluble in pyridine. This substance gave a white residue upon ignition in a flame which, when dissolved in alkali and partially neutralized with acetic acid, gave a white precipitate upon treatment with hydrogen sulfide. A solution in dilute nitric acid gave a white precipitate when silver nitrate solution was added.

Anal. Calcd. for $C_{20}H_{24}N_2Cl_2Zn$: C, 56.03; H, 5.64; N, 6.54. Found: C, 56.23; H, 5.60; N, 6.80.

Addition of hexane to a pyridine solution of the compound precipitated 92% of the theoretical quantity of zinc chloride as the pyridine complex. Removal of solvent at reduced pressure left a colorless, viscous oil which decomposed rapidly in the presence of air. I.R. (CCl_4): 3350 (NH, shifted to 3140 cm.$^{-1}$ in the $ZnCl_2$ complex), 1670 cm.$^{-1}$ (C=N).

Hydrolysis of the diamine–zinc chloride complex. Two g. of the Zn complex of VIa was dissolved in 50 ml. of warm 10% hydrochloric acid, the solution neutralized with alkali, and just sufficient dilute hydrochloric acid added to bring about solution. Acetic anhydride (5 ml.) and sodium acetate (5 g.) were then added and the mixture was allowed to stand in an ice bath for 15 min. Addition of 10 ml. of concd. hydrochloric acid and filtration gave 0.18 g. of *p*-acetotoluidine, m.p. and mixture m.p. 147.5–148.5°. Adjustment of the filtrate to *p*H 6 gave a solid precipitate (1.13 g., m.p. 102–115°) which, after crystallization from ethanol, melted at 112–114° and did not depress the m.p. of VI.

Ring-closure of VIa. To the oily residue, obtained from 1.00 g. of the complex by removal of zinc chloride with pyridine as described above, were added 25 ml. of Cellosolve and 0.53 g. of anhydrous magnesium chloride. After heating at reflux for 4 hr. and working up in the usual manner, 0.32 g. of crude 6-methyl-1,2,3,4-tetrahydrocarbazole (XIX) (m.p. 140–145°) was obtained. Crystallization from aqueous methanol raised the melting point to 145–146°.

Preparation of tetrahydrocarbazoles. Method A. 5,6,7,8-Tetrahydro-3,4-benzocarbazole (XIV). In a 300-ml. three-neck flask which had been swept out with nitrogen were placed 10.0 g. (0.0418 mole) of 2-(2-naphthylamino)cyclohexanone and 200 ml. of a 20% solution of anhydrous zinc chloride in absolute ethanol. The resulting solution was heated under reflux, in an atmosphere of nitrogen, for 8 hr. The cooled bright red solution was poured into a stirred mixture of 300 ml. of concd. hydrochloric acid and 700 g. of cracked ice. The mixture was filtered, washed with dilute hydrochloric acid and water, and dried in a vacuum desiccator. The yield was 8.5 g. (92%) of buff crystalline solid, m.p. 135–137°. Crystallization from aqueous ethanol gave 6.4 g. of nearly colorless needles, m.p. 137–137.5°, undepressed by admixture with an authentic specimen.[12]

5,6,7,8-Tetrahydro-1,2-benzocarbazole was obtained in 97% yield, m.p. 138–139.5°, in the same manner except that the reflux period was 12 hr. Crystallization from aqueous ethanol provided white plates, m.p. 140–140.5°.[25]

A *picrate* was obtained as brown needles from ethanol, m.p. 170–171°.[26]

Method B. A solution of 0.025 mole of the appropriate aniline derivative and 0.05 mole of anhydrous magnesium chloride in 50 ml. of Cellosolve (or 30 ml. of methylcellosolve and 20 ml. of butylcellosolve) was prepared by boiling under nitrogen for 15 min. After slight cooling, 0.025 mole of the arylaminocyclohexanone was added and the solution heated under reflux in a nitrogen atmosphere for 4 hr. The cooled reaction mixture was then added dropwise to a vigorously stirred mixture of 125 g. of cracked ice and 50 ml. of concd. hydrochloric acid. After stirring for 1 hr. the mixture was filtered, washed with 10% hydrochloric acid and water, and dried in a vacuum desiccator. The crude product was decolorized with Norit and crystallized from aqueous methanol.

6-Phenyltetrahydrocarbazole (XXII) required a modified version of Method B. A mixture of 6.00 g. (0.0227 mole) of 2-(*p*-biphenylylamino)cyclohexanone, 1.92 g. (0.0113 mole) of *p*-aminobiphenyl, 10.8 g. (0.113 mole) of anhydrous magnesium chloride, 100 ml. of butylcellosolve, and 20 ml. of methylcellosolve was refluxed under nitrogen for 8 hr. The cooled reaction mixture was then added slowly to a stirred mixture of 350 g. of cracked ice, 200 ml. of water, and 90 ml. of glacial acetic acid. After standing for several hours, the precipitated product was filtered and washed with 15% acetic acid, 40% aqueous methanol containing 0.5% hydrochloric acid, and finally with water. The yield of crude product was 6.10 g. The impure material was treated with Norit in boiling alcohol, filtered, and 5.2 g. of picric acid in the minimum amount of boiling alcohol were added to the filtrate. The yield of powdery, brown *picrate*, m.p. 151–153.5°, was 6.82 g. (63%). After crystallization from ethanol, 5.33 g. of brown crystals, melting at 153–154°, were recovered. Slow addition of an acetone solution of the picrate to 300 ml. of concd. aqueous ammonia, with stirring and cooling, in an ice bath, followed by filtration, washing with ammonia and water, and drying *in vacuo*, gave 2.54 g. (45%) of buff crystalline powder, m.p. 144–151°. Two crystallizations from ethanol water yielded pale yellow plates, m.p. 153–154° (*in vacuo*).

9-Ethyltetrahydrocarbazole (XXVI). To a solution prepared by boiling 4.4 g. (0.046 mole) of anhydrous magnesium chloride and 2.80 g. (0.0230 mole) of ethylaniline with a mixture of 40 ml. of butylcellosolve and 20 ml. of methylcellosolve, were added 5.00 g. (0.0230 mole) of crude 2-*N*-ethylanilinocyclohexanone. After refluxing under nitrogen for 4 hr., the reaction mixture was cooled, poured into 250 ml. of 10% hydrochloric acid, and extracted four times with a total of 200 ml. of benzene. The combined benzene extracts were then washed with dilute hydrochloric acid, water, and sodium carbonate solution and dried over sodium sulfate. The residue remaining after removal of the benzene was converted to the picrate with 5.9 g. of picric acid in the minimum amount of hot ethanol. Filtration and washing with cold alcohol provided 7.3 g. (75%) of crude *picrate* as brown needles, m.p. 90–93°. Since this compound appeared to be quite unstable no attempt was made to purify it further. It was reported to melt at 92–92.5°.[27]

The picrate was decomposed by stirring for 24 hr. with 750 ml. of 10% sodium carbonate solution. The resulting oily mixture was extracted with ether (250 ml.) and the extract washed with 5% sodium carbonate and water and dried over sodium sulfate. After removal of the ether, the yield of light amber oil was 2.86 g. (61%), n_D^{25} 1.5858. The infra-

(23) W. A. Noyes, *Am. Chem. J.*, **10**, 475 (1888).

(24) L. Gattermann and A. Kaiser, *Ber.*, **18**, 2600 (1885) reported m.p. 7°.

(25) W. Borsche, A. Witte, and W. Bothe, *Ann.*, **359**, 49 (1908), reported 140°.

(26) S. H. Oakeshott and S. G. P. Plant, *J. Chem. Soc.*, 1842 (1928), reported 172°.

(27) H. Adkins and H. L. Coonradt, *J. Am. Chem. Soc.*, **63**, 1563 (1941).

red spectrum had no bands in the 3.0 (NH) or 5.8μ (CO regions.

A sample for analysis was prepared by distillation at reduced pressure, giving a viscous yellow oil with a faint rubber-like odor and blue fluorescence in daylight, b.p. 105–106°/0.1 mm., n_D^{25} 1.5912; n_D^{25} 1.5933. (Adkins and Coonradt[27] reported n_D^{25} 1.5498 for a product obtained by catalytic hydrogenation of 9-ethylcarbazole.)

Method C. A mixture of 0.01 mole of the arylaminocyclohexanone, 0.01 mole of the appropriate amine, 0.002 mole of concentrated sulfuric acid, and 30 ml. of Cellosolve was refluxed in an atmosphere of nitrogen for 4 hr. The resulting solution was poured into a mixture of 125 g. of cracked ice and 50 ml. of concentrated hydrochloric acid, and the crude product filtered, washed with dilute hydrochloric acid and water, and crystallized from aqueous ethanol.

8-Chloro-5-methyltetrahydrocarbazole (XXV) was prepared by a modification of the above procedure. A mixture of 23.77 g. (0.100 mole) of 2-(2-chloro-5-methylanilino)cyclohexanone, 14.1 g. (0.100 mole) of 4-chloro-3-aminotoluene, 2.55 g. (0.025 mole) of concd. sulfuric acid and 100 ml. of butylcellosolve was refluxed under nitrogen for 24 hr. The cooled reaction mixture was poured into 1 l. of 10% hydrochloric acid and the resulting violet colored mixture extracted with three 150-ml. portions of chloroform. The combined chloroform extracts were washed with two 500-ml. portions of 10% hydrochloric acid, two 500-ml. portions of water, and two 250-ml. portions of dilute sodium sulfite solution. After adding a few crystals of hydroquinone and drying over Drierite, the solvent was removed at reduced pressure. To the residual oil were added 25.0 g. of picric acid dissolved in 25 ml. of boiling ethanol. The brick-red crystals of the *picrate* were removed by filtration and washing with cold ethanol. The crude material weighed 34.6 g. (77%) and melted at 148–151°. Crystallization from ethanol gave, in two crops, 31.7 g. (71%) of picrate, m.p. 151–152°.

To 1.5 l. of concentrated aqueous ammonia, cooled in an ice bath, was added slowly with stirring, a solution of the picrate in 250 ml. of warm acetone. After stirring for 1 hr., the orange precipitate was removed by filtration, washed with ammonia and water, dissolved in 150 ml. of acetone, and reprecipitated by pouring into 1 l. of ice water. Filtration, washing with water, and drying *in vacuo* provided 15.3 g. (70%) of XXV as amber crystals, m.p. 68.5–69.5° (*in vacuo*). Two crystallizations from methanol water gave an analytical sample of small colorless needles, m.p. 69–70° (*in vacuo*).

5-Methyl-1,2,3,4-tetrahydrocarbazole (XX). To a solution of 0.50 g. (0.0023 mole) of XXV and 0.18 g. (0.0027 mole) of potassium hydroxide in 25 ml. of methanol was added 0.20 g. of 5% palladium-charcoal catalyst. The reaction flask was flushed first with nitrogen then with hydrogen. Hydrogen consumption began as soon as the stirrer was started and ceased after 1.25 hr. when 67 ml. had been taken up. After the catalyst was removed by filtration, the product was precipitated by pouring the methanol solution into cold water. After filtration, washing with water, and drying in a vacuum desiccator the product weighed 0.40 g. (95%) and melted at 150–150.5° (*in vacuo*). A mixture of XX and XVIII melted at 95–118°.[10]

11-Hydroperoxy-5-methyl-1,2,3,4-tetrahydrocarbazolenine (XXa). A solution of 0.182 g. of XX in 30 ml. of hot petroleum ether (b.p. 63–99°) was allowed to stand in a loosely stoppered flask. A precipitate appeared after 10 min. and, after 8 hr., the mixture was filtered and washed with cold hexane, yielding 0.168 g. (77%) of colorless, crystalline hydroperoxide, m.p. 126° (dec.) (Coldham. Lewis, and Plant[16] reported m.p. 125°). The hydroperoxide was soluble in dilute aqueous mineral acid and immediately liberated iodine from acidified potassium iodide solution. The I.R. showed a strong OH stretching band at 3050 cm.$^{-1}$ and a weak OH deformation band at 1020 cm.$^{-1}$, but no NH band in the 3400 cm.$^{-1}$ region.

Anal. Calcd. for $C_{13}H_{15}NO_2$: N, 6.45. Found: N, 6.44.

11-Hydroperoxy-7-methyl-1,2,3,4-tetrahydrocarbazolenine. A hot solution of 0.100 g. of XVIII in 10 ml. of petroleum ether (b.p. 63–99°) was allowed to stand in a loosely stoppered flask overnight. Filtration and washing with hexane gave 0.103 g. (86%) of fine white needles, m.p. 124° (dec.). The hydroperoxide was insoluble in sodium hydroxide solution but very soluble in 10% hydrochloric acid and liberated iodine immediately from acidified potassium iodide solution. The infrared spectrum had no NH band but had a broad band at 3060 cm.$^{-1}$ as well as a band at 1050 cm.$^{-1}$ There was no indication of the presence of any of the isomeric hydroperoxide in the I.R. spectrum.

Anal. Calcd. for $C_{13}H_{15}NO_2$: N, 6.45. Found: N, 6.55.

Color test for tetrahydrocarbazoles. Approximately 5 mg. of the compound to be tested was dissolved in about 1 ml. of glacial acetic acid and shaken with a 2% solution of bromine in glacial acetic acid added dropwise until a definite color persisted. The initial color was usually the pale yellow of bromine but occasionally a light green formed almost immediately. The solution was then allowed to stand in an open test tube for 5–10 min. If a green or blue color had developed, the test was considered positive. If the color had faded, a few more drops of bromine solution were added and the solution warmed on the steam bath for 2–3 min. When the sample was a carbazole the color was generally bleached by heating, but if it were a tetrahydrocarbazole the color changed to a green, blue-green, or blue. Occasionally a purple color was observed, but this always changed to green or blue upon addition of a few additional drops of bromine solution. In most cases the colors were not stable and slowly changed to gray or brown, sometimes with the appearance of a precipitate.

General procedure for dehydrogenation. For each gram of tetrahydrocarbazole, 10 ml. of xylene and 0.25–0.4 g. of 30% palladium on charcoal catalyst were used. After heating the mixture under reflux for 12 hr., it was cooled and in those cases in which a precipitate appeared, sufficient ethyl acetate to dissolve the precipitate was added. The catalyst was removed by filtration and washing with ethyl acetate. The combined filtrate and washings were evaporated to a thick slurry by warming on the steam bath in a stream of air. The slurry was then diluted with an equal volume of hexane, cooled in an ice bath, filtered, and washed with hexane. With the exception of the tetrahydrobenzocarbazoles which were more resistant to dehydrogenation, the crude carbazoles had melting points which were only 1 or 2° below these of the analytical samples. All these were crystallized from ethanol except XXVI and XXXIII, which were crystallized from xylene and methanol, respectively.

1,2-Benzocarbazole. In this case the usual procedure gave a very impure product either because of a greater-than-usual resistance to dehydrogenation or to low activity of the catalyst. From 5.00 g. of crude 5,6,7,8-tetrahydro-1,2-benzocarbazole (XV) (m.p. 138–139.5°), 4.13 g. of product melting at 185–200° were obtained. This material was again dehydrogenated using cumene in place of xylene as the solvent. The yield was 3.65 g. (74% over-all) of 1,2-benzocarbazole, m.p. 231–233°. Crystallization from ethanol gave colorless plates, m.p. 232–233°. (Borsche *et al.*[25] have reported this compound to melt at 225° and Oakeshott and Plant[26] give m.p. 225–226°.)

Anal. Calcd. for $C_{16}H_{11}N$: C, 88.45; H, 5.10; N, 6.45. Found: C, 88.22; H, 4.96; N, 6.73.

The *picrate* formed in maroon needles from alcohol, m.p. alcohol, m.p. 189–191° (dec.). This derivative has been reported[25] to melt at 185°.

Anal. Calcd. for $C_{22}H_{14}N_4O_7$: N, 12.56. Found: N, 12.60.

Abbreviated procedure for preparation of carbazoles. The following procedure for the preparation of carbazoles is typical. A mixture of 6.63 g. (0.0500 mole) of 2-chlorocyclohexanone (I), 4.66 g. (0.0500 mole) of aniline, 10 g. of anhydrous sodium carbonate, 0.65 g. (0.0050 mole) of quinoline, and 30 ml. of Cellosolve was stirred and heated under reflux until the evolution of carbon dioxide had ceased (0.75 hr.).

The reaction mixture was cooled under nitrogen, filtered, and the filter cake washed with three 10-ml. portions of Cellosolve. To the combined filtrate and washings were added 2.33 g. (0.025 mole) of aniline and 12.0 g. (0.125 mole) of anhydrous magnesium chloride, washed into the flask with 15 ml. of Cellosolve. After heating under reflux in an atmosphere of nitrogen for 4 hr. the solution was cooled and allowed to run slowly into a stirred mixture of 100 ml. of concd. hydrochloric acid and 250 g. of cracked ice. After standing overnight, the mixture was filtered and washed with dilute hydrochloric acid, water, and twice with 50% aqueous ethanol. After drying in a vacuum desiccator, the crude *tetrahydrocarbazole* weighed 7.29 g. (85%) and melted at 110–116°.

Dehydrogenation of 2.50 g. of this material in the usual manner gave 2.12 g. (74%, based on 2-chlorocyclohexanone) of XXVII, white plates, m.p. 244–246.5°.

By a similar procedure *1-methylcarbazole* was obtained in 83% yield (crude product, m.p. 118–121°; the yield of purified XXVIII, m.p. 120–121°, was 65%) and *3,4-benzocarbazole* in 40% yield (m.p. 133–134.5°), based on 2-chlorocyclohexanone.

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[CONTRIBUTION NO. 873 FROM THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

Syntheses of Some Methyl Substituted 3,4-Benzocarbazoles[1,2]

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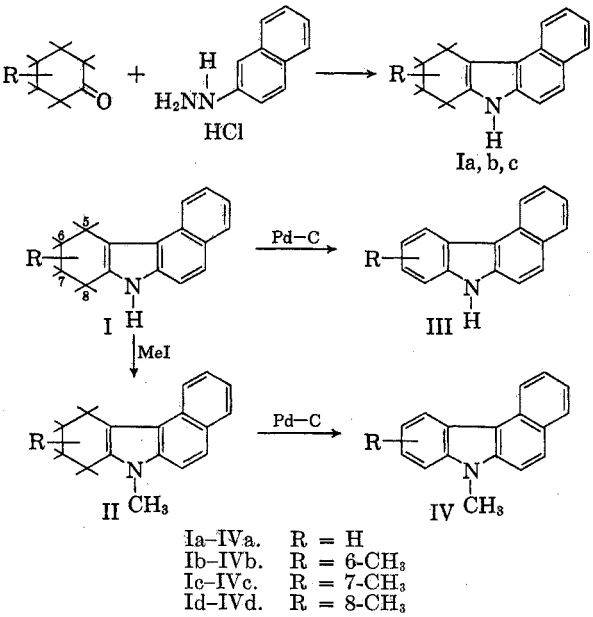
A series of methyl and dimethyl 3,4-benzocarbazoles were prepared by dehydrogenation of the respective 5,6,7,8-tetrahydro-3,4-benzocarbazoles. The latter compounds were obtained by a modified Fischer-Borsche reaction. The product of the reaction of 3-methylcyclohexanone and β-naphthylhydrazine was proved to be 7-methyl-5,6,7,8-tetrahydro-3,4-benzocarbazole, rather than the alternate possible 5-methyl isomer.

The fact that the dibenzocarbazoles are carcinogenic[6–8] has stimulated interest in the synthetic[9,10] and theoretical[11] study of carbazoles. It is known that the tumor producing activity of 1,2,5,6-dibenzanthracene is inhibited by 1,2,5,6-dibenzocarbazole.[12] Partially hydrogenated carbazoles are also of interest because of potential anticarcinogenic activity.[13]

Accordingly, we have undertaken the synthesis of a series of methyl substituted 3,4-benzocarbazoles and 5,6,7,8-tetrahydro-3,4,benzocarbazoles, for use in biological experiments. (Table I). As a result, an extremely convenient technique, involving a modified Fisher-Borsche synthesis,[14] has been developed for the preparation of 5,6,7,8-



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