[CONTRIBUTION FROM THE CANCER RESEARCH LABORATORY, UNIVERSITY OF FLORIDA]

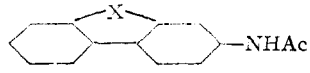
# Synthesis and Ultraviolet Absorption Spectra Studies of 2,3- and 3,4-Disubstituted Carbazoles[1]

BY EUGENE SAWICKI

RECEIVED SEPTEMBER 11, 1953

Several possibly carcinogenic derivatives of 2-aminocarbazole and some 2,3- and 3,4-disubstituted carbazole compounds have been prepared. The absorption spectra of 2,3- and 3,4-disubstituted carbazole derivatives are discussed. The nitrations of 2-acetylamino- and 3-carbethoxyamino-9-methylcarbazole have been spectrally shown to take place in the 3- and 4-positions, respectively.

In a continuation of a study of the chemical, physical and biological properties of carcinogenic amines and allied compounds the preparation and spectral properties of some new carbazole derivatives were investigated. 4-Acetylaminobiphenyl,[2] 2-acetylaminofluorene,[3] 2-acetylaminofluorenone,[4] 3-acetylaminodibenzofuran,[5] 3-acetylaminodibenzothiophene,[5] 3-acetylaminodibenzothiophene-5-oxide,[5] 2-acetylaminophenanthrene[4] and 2-acetylamino-9,10-dihydrophenanthrene[4] (I) have been shown to be carcinogenic. These active compounds have the amino group in the extended para position.




I, X = $H_2$, $CH_2$, C=O, O, S, S=O, CH=CH, $CH_2$—$CH_2$
II, X = Se, NH, NMe

Compounds such as 1-naphthylamine,[6] 3-dimethylaminocarbazole,[7] 4-acetylaminofluorene,[8] 3-aminophenanthrene,[9] 9-aminophenanthrene[9] and 9-aminoanthracene[10] which do not have an amino group in the extended para positions have been stated to be non-carcinogenic under the conditions of the authors' experiments and thus can be tentatively considered as inactive.

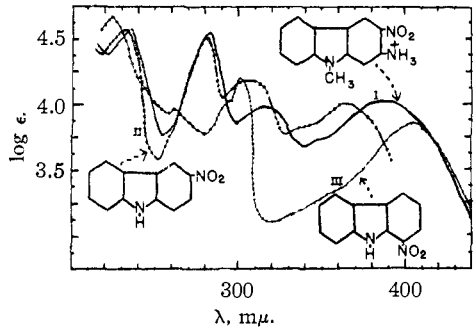



Fig. 1.—I, 2-amino-3-nitro-9-methylcarbazole in 50% alcoholic 6 *N* hydrochloric acid; II, 3-nitrocarbazole; III, 1-nitrocarbazole.

Recently the potentially carcinogenic 3-acetylaminodibenzoselenophene (II, X = Se) was prepared.[11] To further broaden our knowledge of this particular field of study the potentially carcinogenic 2-acetylamino-9-methylcarbazole (AAMC) (II X = NMe) and 2-acetylaminocarbazole (II, X = NH) were synthesized. As ortho substitution is probably of some importance in carcinogenesis,[12] some ortho substituted derivatives of AAMC were prepared.

For purposes of comparison the chemistry and spectra of the potentially non-carcinogenic 3-acetylamino-9-methylcarbazole and its derivatives were also investigated.

The deacetylation and reduction of nitro AAMC forms a diamine which reacts with selenium dioxide to give a red compound. This product gives a qualitative test for selenium and a red-violet color with concentrated sulfuric acid. It is evident that a piaselenole has been formed. Nitration of AAMC must have taken place in the 1- or 3-position. In Fig. 1 it can be seen that the new nitro-2-amino-9-methylcarbazole hydrochloride is spectrally similar to 3-nitrocarbazole[13] and not to 1-nitrocarbazole.[13] In addition the spectra of the piaselenoles derived from the new nitro AAMC and 3-amino-2-nitrocarbazole are closely similar while different from the spectrum of the piaselenole derived from 3-amino-4-nitro-9-methylcarbazole, Fig. 2. On the basis of these facts it is concluded that the nitration of 2-acetylamino-9-methylcarbazole takes place in the 3-position.

Most piaselenoles studied by the author have a high intensity low energy band with a shoulder at the visible end of the spectrum.[11,14] In the piaselenole derived from 3-nitro AAMC the shoulder band apparently has been pushed much further into the visible so that it becomes a separate distinct band, Fig. 2. The absorption spectra of 3-nitro AAMC and its deacetylated derivative are shown in Fig. 3. In the nitroamine the shoulder at the visible end of the spectrum (~ λ 440) is a moderate intensity low energy band which has consistently been found in the spectra of *o*-nitroaromatic amines.[11,14] In the usual case the *o*-nitroamine band is well defined. The band at 395 mμ is to a

(1) This investigation was supported by research grant C-1308 from the National Cancer Institutes of the National Institutes of Health, U. S. Public Health Service.

(2) R. B. Sandin, R. Melby, A. S. Hay, R. N. Jones, H. C. Miller and J. A. Miller, THIS JOURNAL, **74**, 5073 (1952).

(3) R. H. Wilson, F. DeEds and A. J. Cox *Cancer Research*, **1**, 595 (1941).

(4) J. A. Miller, E. C. Miller, R. B. Sandin and H. P. Rusch, *ibid.*, **12**, 283 (1952).

(5) E. C. Miller, J. A. Miller, R. B. Sandin and R. K. Brown, *ibid.*, **9**, 504 (1949).

(6) J. L. Hartwell, "Survey of Compounds Which Have Been Tested for Carcinogenic Activity," United States Government Printing Office, Washington, D. C., 1951, p. 101.

(7) J. A. Miller and E. C. Miller, *J. Exptl. Med.*, **87**, 139 (1948).

(8) J. H. Weisburger, E. K. Weisburger and H. P. Morris, THIS JOURNAL, **74**, 4540 (1952).

(9) Reference 6, p. 110.

(10) Reference 6, p. 109.

(11) E. Sawicki and F. E. Ray, *J. Org. Chem.*, **18**, 946 (1953).

(12) A. L. Walpole, M. H. C. Williams and D. C. Roberts, *Brit. J. Ind. Med.*, **9**, 255 (1952).

(13) W. A. Schroeder, P. E. Wilcox, K. N. Trueblood and A. O. Dekker, *Anal. Chem.*, **23**, 1740 (1951).

(14) E. Sawicki, unpublished work.

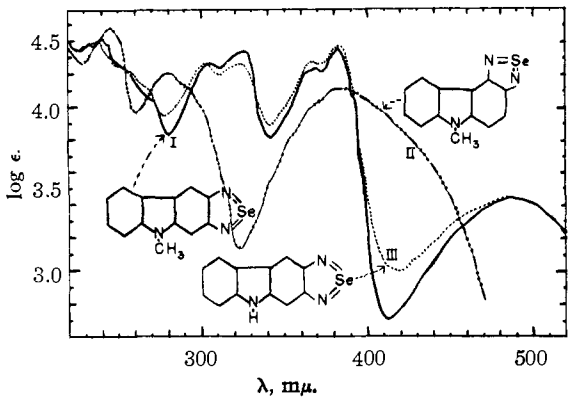



Fig. 2.—I, 5-methyl-5H-indolo[2,3-f]piaselenole; II, 6-methyl-6H-indolo[3,2-e]piaselenole; III, 5H-indolo[2,3-f]-piaselenole. Log ε for III is approximate as only a minute amount of compound was available for study.

large extent a *p*-nitroamine band. This is consistent with the fact that for the same parent hydrocarbon the *p*-nitroamino band is of greater intensity and lower wave length than is the *o*-nitroamino band.[14] In 3-nitro AAMC the *o*-nitroamino shoulder has practically disappeared and the spectrum of this compound resembles that of 3-nitrocarbazole.

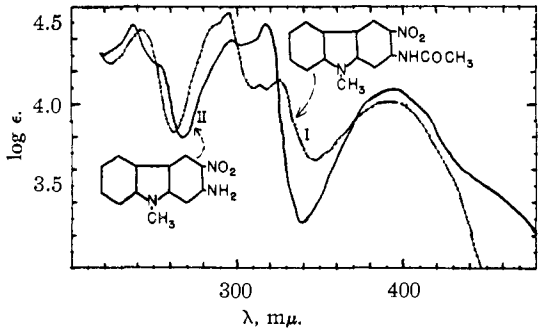



Fig. 3.—I, 2-acetylamino-3-nitro-9-methylcarbazole; II, 2-amino-3-nitro-9-methylcarbazole.

The nitration of 3-carbethoxyamino-9-methylcarbazole followed by deacylation, reduction and reaction with selenium dioxide gave a piaselenole, the absorption spectrum of which is shown in Fig. 2. This compound shows its low energy high intensity piaselenole band at 380–386 mμ. The spectra of nitro-3-carbethoxyamino-9-methylcarbazole and nitro-3-amino-9-methylcarbazole hydrochloride, Fig. 4, are remarkably similar and seem to show a steric effect. This could only be understandable if the nitro group were ortho to the biphenyl linkage. In that respect these compounds resemble 2-nitrobiphenyl[15] spectrally, Fig. 4. If the nitro group of nitro-3-amino-9-methylcarbazole were in the 2-position, the compound would show a very close spectral resemblance to the known 3-amino-2-nitrocarbazole.[16] A spectral comparison of these compounds, Fig. 5, shows that they are not very closely similar spectroscopically. This is

(15) D. F. DeTar and H. J. Scheifele, Jr., THIS JOURNAL, **73**, 1442 (1951).

(16) G. Anderson and N. Campbell, *J. Chem. Soc.*, 2904 (1950). This compound was generously supplied by Dr. G. Anderson.

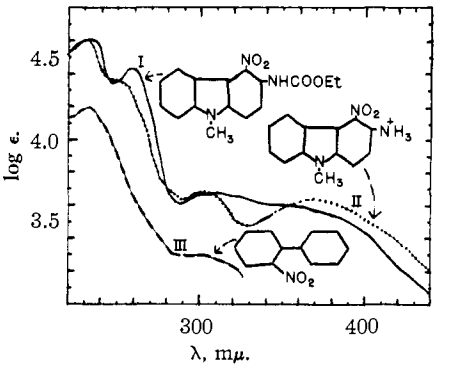



Fig. 4.—I, 3-carbethoxyamino-4-nitro-9-methylcarbazole; II, 3-amino-4-nitro-9-methylcarbazole in 50% alcoholic 2 *N* hydrochloric acid; III, 2-nitrobiphenyl.

further evidence that the nitro group in this new derivative is ortho to the biphenyl linkage. As

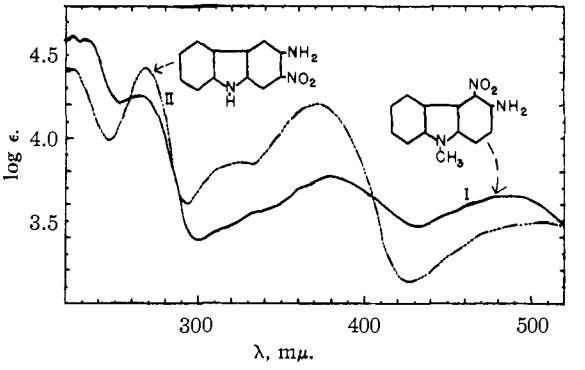



Fig. 5.—I, 3-amino-4-nitro-9-methylcarbazole; II, 2-nitro-3-aminocarbazole.

one would expect, the spectra of 2-nitrocarbazole and 3-amino-2-nitrocarbazole hydrochloride are closely similar, Fig. 6. The spectrum of 2-nitro-9-methylcarbazole is almost identical with that of 2-nitrocarbazole. Comparison of these spectra with that of the new 3-amino-4-nitro-9-methylcarbazole hydrochloride, Fig. 4, shows again that the nitro group cannot be in the 2-position. On the basis of these facts it is concluded that the nitration of 3-carbethoxyamino-9-methylcarbazole takes place in the 4-position.

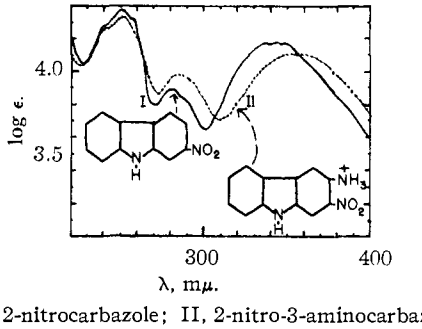



Fig. 6.—I, 2-nitrocarbazole; II, 2-nitro-3-aminocarbazole in 50% alcoholic 1 *N* hydrochloric acid.

Both 3-amino-4-nitro-9-methylcarbazole and 2-amino-3-nitrocarbazole show well-developed *o*-nitroamino bands at 481 and 500–504 mμ, respectively. Protonation destroys these bands as seen

for the 3,4-derivative in Fig. 4 and for the 2,3-derivative in Fig. 6.

Carbazole and dibenzothiophene are iso-$\pi$-electronic and so are spectrally similar.[17] Analogous derivatives of dibenzothiophene and carbazole should be iso-$\pi$-electronic and consequently spectrally similar. The similarity of these derivatives in the ultraviolet and visible spectra has been shown recently.[18] Comparison of the spectra of 2-aminodibenzothiophene and the iso-$\pi$-electronic 3-amino-9-methylcarbazole shows this spectral similarity also, Fig. 7. Actually the spectra of these compounds resemble that of carbazole and dibenzothiophene.[18] It is very likely that the free electrons on the amino nitrogen interact mainly with the $\pi$-electrons of the adjacent ring and the free electrons of the hetero atom in the middle ring. This transverse polarization has the greatest bathochromic effect on the low intensity bands of dibenzothiophene and carbazole near 320 m$\mu$.

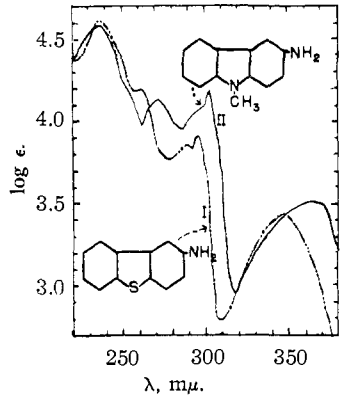



Fig. 7.—I, 2-aminodibenzothiophene; II, 3-amino-9-methylcarbazole.

On the other hand, the spectra of 3-aminodibenzothiophene and 2-aminocarbazole, Fig. 8, show points of similarity, but also some differences.

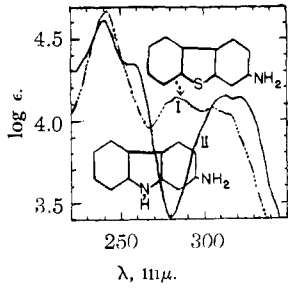



Fig. 8.—I, 3-aminodibenzothiophene; II, 2-aminocarbazole.

It is very probable that the free electrons on the amino nitrogen of either molecule can interact freely with the $\pi$-electrons of the entire parent compound. The consequent longitudinal polarization has the greatest bathochromic effects on the middle bands of dibenzothiophene and carbazole ($\lambda$ 250–290 m$\mu$). This bathochromic shift is so great that the low intensity bands of dibenzothiophene and carbazole at approximately 320 m$\mu$ are covered over. As a result the spectra of these amines are entirely different from that of dibenzothiophene and carbazole.

**Acknowledgment.**—The author wishes to express his appreciation to Dr. F. E. Ray, director of the Cancer Research Laboratory, for his interest and full coöperation.

## Experimental[19]

**2-Aminocarbazole.**—To a solution of 1.06 g. of 2-nitrocarbazole[20] in 25 ml. of boiling alcohol was added a solution of 4.3 g. of stannous chloride in 5 ml. of hydrochloric acid. Ten ml. of concentrated hydrochloric acid was added and the solution was allowed to cool. The precipitate was treated with alkali and crystallized from xylene to give 0.5 g. (55%) of colorless crystals, m.p. 238.0–239.5°, lit. m.p. 238–239°.[16]

**2-Acetylaminocarbazole.**—A hot solution of 2-aminocarbazole in xylene was treated with acetic anhydride by standard procedure. Crystallization from heptane or aqueous alcohol gave an 85% yield of colorless crystals, m.p. 237–238°.

*Anal.* Calcd. for $C_{14}H_{12}N_2O$: N, 12.5. Found: N, 12.2.

**2-Amino-9-methylcarbazole.**—A solution of 60 g. of stannous chloride in 100 ml. of concentrated hydrochloric acid was added to a hot suspension of 11.3 g. of 2-nitro-9-methylcarbazole[21] in 100 ml. of hot alcohol. The tin complex was isolated and decomposed by alkali into the free amine. Crystallization from heptane gave 8.2 g. (84%) of colorless needles, m.p. 135–136.5°.

*Anal.* Calcd. for $C_{13}H_{12}N_2$: N, 14.3. Found: N, 14.2.

**2-Trifluoroacetylamino-9-methylcarbazole.**—Trifluoroacetic anhydride[22] was treated with a benzene solution of 2-amino-9-methylcarbazole by the usual procedure. Crystallization from aqueous alcohol gave a 92% yield of colorless needles, m.p. 206–208°.

*Anal.* Calcd. for $C_{15}H_{11}F_3N_2O$: N, 9.59. Found: N, 9.46.

**2-Acetylamino-9-methylcarbazole.**—The reaction of a benzene solution of 2-amino-9-methylcarbazole with an equivalent of acetic anhydride gave this compound. Crystallization from alcohol gave an 88% yield of colorless needles, m.p. 237–238°.

*Anal.* Calcd. for $C_{15}H_{14}N_2O$: N, 11.8. Found: N, 11.5.

**2-Acetylamino-3-nitro-9-methylcarbazole.**—To a stirred suspension of 8.6 g. of 2-acetylamino-9-methylcarbazole in 150 ml. of acetic acid at 25° was added 18 ml. of dilute nitric acid (d. 1.5 diluted 1:10 with acetic acid). The mixture was allowed to stand one hour at 25–30°. The yellow precipitate, crystallized twice from methyl cellosolve, gave 4.0 g. (39%) of yellow needles, m.p. 236–237°.

*Anal.* Calcd. for $C_{15}H_{13}N_3O_3$: C, 63.6; H, 4.59; N, 14.8. Found: C, 63.7; H, 4.57; N, 14.8.

**2-Amino-3-nitro-9-methylcarbazole.**—The hydrolysis of 2-acetylamino-3-nitro-9-methylcarbazole was accomplished by refluxing its methyl cellosolve–hydrochloric acid solution for one hour. The golden-yellow needles of the hydrochloride were easily decomposed to the free amine by excess water. Crystallization from benzene–heptane gave a 95% yield of long red-orange needles changing to chunky dark red crystals on standing, m.p. 195–196°.

*Anal.* Calcd. for $C_{13}H_{11}N_3O_2$: N, 17.4. Found: N, 17.2.

**2,3-Diamino-9-methylcarbazole.**—A solution of 2.25 g. of stannous chloride in 4 ml. of concentrated hydrochloric acid was added to a hot solution of 0.45 g. of 2-amino-3-nitro-9-methylcarbazole in 4 ml. of methyl cellosolve. The mixture was refluxed for 0.5 hour and then cooled. The precipitate was suspended in water, made alkaline and filtered. Extraction of the residue with heptane gave 0.24 g. (61%) of a gray gelatinous solid, m.p. 179–180°.

*Anal.* Calcd. for $C_{13}H_{13}N_3$: N, 19.9. Found: N, 19.3.

(17) J. R. Platt, *J. Chem. Phys.*, **19**, 101 (1951).

(18) E. Sawicki, *J. Org. Chem.*, **18**, 1492 (1953).

(19) All melting points are uncorrected. Analyses are by the Rowland Chemical Laboratories, 1330 Talleyrand Ave., Jacksonville, Fla.

(20) P. A. S. Smith and B. B. Brown, THIS JOURNAL, **73**, 2435 (1951).

(21) E. Sawicki, *ibid.*, **75**, 4106 (1953).

(22) Obtained from the Minnesota Mining and Manufacturing Co., St. Paul 6, Minn.

**5-Methyl-5H-indolo[2,3-f]piaselenole.**—To a stirred solution of 0.21 g. of 2,3-diamino-9-methylcarbazole in 4 ml. of hot alcohol was added 0.12 g. of selenium dioxide. The mixture was refluxed for 5 minutes and allowed to cool. The red crystals were crystallized from xylene to give 0.25 g. (88%) of red needles, m.p. 243–244°. The compound dissolved in concentrated sulfuric acid with a dark yellow color which turned green on heating and dark violet on the addition of a little water.

*Anal.* Calcd. for $C_{13}H_9N_3Se$: N, 14.7. Found: N, 14.5.

**3-Nitro-9-methylcarbazole.**—Two and a half grams of nitric acid (d. 1.49) in 5 ml. of acetic acid was added dropwise to a stirred mixture of 6.1 g. of N-methylcarbazole[23] in 100 ml. of acetic acid at 0–10°. After standing one hour at 0–10° the reaction mixture was poured into excess water. Crystallization from aqueous methyl cellosolve and then alcohol gave 6.1 g. (80%) of long glossy yellow needles, m.p. 171–172°, lit. m.p. 170–172°.[24]

**3-Amino-9-methylcarbazole.**—This compound was prepared in a 70–80% yield by the procedure used for the 2-amino isomer. Crystallization from methanol or heptane gave colorless needles, m.p. 173–174°, lit. m.p. 171–173°.[24]

**3-Acetylamino-9-methylcarbazole.**—The amine in benzene solution was acetylated with acetic anhydride by standard procedure. Crystallization from aqueous methanol gave a 95% yield of colorless needles, m.p. 210°.

*Anal.* Calcd. for $C_{15}H_{14}N_2O$: C, 75.63; H, 5.89; N, 11.8. Found: C, 75.52; H, 5.67; N, 11.8.

**3-Trifluoroacetylamino-9-methylcarbazole.**—The amine in benzene solution was acylated with trifluoroacetic anhydride by standard procedure. Crystallization from heptane gave a 92% yield of colorless needles, m.p. 184–185°.

*Anal.* Calcd. for $C_{15}H_{11}F_3N_2O$: N, 9.59. Found: N, 9.77.

**3-Carbethoxyamino-9-methylcarbazole.**—The amine in ice-cold pyridine solution was treated with ethyl chlorocarbonate by standard procedure. Crystallization from heptane gave an 86% yield of colorless needles, m.p. 110.0–110.5°.

(23) T. S. Stevens and S. H. Tucker, *J. Chem. Soc.*, **123**, 2140 (1923).

(24) D. H. Hey and R. D. Mulley, *ibid.*, 2276 (1952).

*Anal.* Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.64; H, 5.97; N, 10.4. Found: C, 71.80; H, 6.06; N, 10.4.

**3-Carbethoxyamino-4-nitro-9-methylcarbazole.**—To a stirred solution of 1.88 g. of 3-carbethoxyamino-9-methylcarbazole in 10 ml. of acetic acid at room temperature was added 3.5 ml. of dilute nitric acid (d. 1.5 diluted, 1:10 with acetic acid). The mixture was allowed to stand an hour. The red crystalline precipitate was crystallized from heptane to give 1.25 g. (57%) of long orange needles, m.p. 184–185°.

*Anal.* Calcd. for $C_{16}H_{15}N_3O_4$: N, 13.4. Found: N, 13.1.

**3-Amino-4-nitro-9-methylcarbazole.**—A suspension of 1 g. of 3-carbethoxyamino-4-nitro-9-methylcarbazole in 12 ml. of methyl cellosolve and 9 ml. of 15% aqueous sodium hydroxide was refluxed for 1 hour. Excess water was added. The precipitate was crystallized from heptane to give 0.68 g. (88%) of red crystals, m.p. 145–146°.

*Anal.* Calcd. for $C_{13}H_{11}N_3O_2$: N, 17.4. Found: N, 17.1.

**3,4-Diamino-9-methylcarbazole.**—Reduction of 3-amino-4-nitro-9-methylcarbazole was achieved by the procedure used for the 2,3-isomer. Crystallization from heptane gave a 78% yield of colorless needles, m.p. 127–128°.

*Anal.* Calcd. for $C_{13}H_{13}N_3$: N, 19.9. Found: N, 19.9.

**6-Methyl-6H-indolo[3,2-e]piaselenole.**—A solution of 0.12 g. of selenium dioxide in 2 ml. of alcohol was added to a hot solution of 0.20 g. of 3,4-diamino-9-methylcarbazole in 5 ml. of alcohol. The solution was refluxed 0.5 hour and then allowed to cool. The yellow-brown crystals were crystallized from benzene–heptane to give 0.22 g. (81%) of yellow crystals, m.p. 180–181°.

*Anal.* Calcd. for $C_{13}H_9N_3Se$: N, 14.7. Found: N, 14.7.

**5H-Indolo[2,3-f]piaselenole.**—This compound was prepared from 2-nitro-3-aminocarbazole by the same methods used for the preparation of the other piaselenoles. As only a small amount of starting product was available, only a minute amount of alcohol-soluble red powdery piaselenole was obtained. This compound, m.p. 243–245°, gave a red-yellow color in concentrated sulfuric acid.

*Anal.* Calcd. for $C_{12}H_7N_3Se$: N, 15.4. Found: N, 14.6.

GAINESVILLE, FLA.

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION, LABORATORY OF ADVANCED RESEARCH, REMINGTON RAND, INC.]

# Synthesis of 4-Alkyl-v-triazoles from Acetylenic Compounds and Hydrogen Azide[1]

BY L. W. HARTZEL AND F. R. BENSON

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Members of the hitherto undescribed class of 4-alkyl-v-triazoles have been synthesized by reaction of substituted acetylenes with hydrogen azide. Absorption spectra and molar refractions for some of these v-triazoles have been obtained.

The synthesis of v-triazoles which involves the combination of hydrogen azide with acetylenic compounds was originated by Dimroth and Fester.[2] These investigators prepared the parent compound by heating an alcoholic solution of hydrazoic acid with an acetone solution of acetylene at 100° for 70 hours. The same reaction has been used to obtain 4-carboxy-, 4-carboxy-5-phenyl-, and 4,5-dicarboxy-v-triazole[3] as well as 4-formyl-v-triazole[4a] and its acetal.[4b] These v-triazole syntheses are similar to those used for the preparation of tetrazoles by the reaction of nitriles with hydrazoic acid.[5] The present article describes the extension of this reaction to monoalkyl acetylenes.

It was found that these ethynyl compounds combine readily with hydrazoic acid in benzene solution by heating in closed vessels at temperatures ranging from 90 to 135° for 29 to 48 hours. In all cases, during the course of the reaction a white solid appeared at the top of the reaction vessels which was identified as ammonium azide. The formation of this material by the decomposition of hydrazoic acid has been described previously.[6] The physical properties, yields and chemical analyses of the 4-alkyl-v-triazoles thus formed are listed in Table I. The members of

(1) This work was performed under a subcontract from Arthur D. Little, Inc., by Remington Rand, Inc., in connection with an Army Ordnance Corps project. Publication of this article has been approved by the Public Information Division, National Military Establishment. Presented before the Division of Organic Chemistry, American Chemical Society, Chicago, September 8, 1953.

(2) O. Dimroth and G. Fester, *Ber.*, **43**, 2219 (1910).

(3) E. Oliveri-Mandala and A. Coppola, *Gazz. chim. ital.*, **40II**, 436 (1910).

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(5) A. Hantzsch and A. Vagt, *Ann.*, **314**, 339 (1901); J. S. Mihina and R. M. Herbst, *J. Org. Chem.*, **15**, 1082 (1950).

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