Experimental

The preparative aspects of the compounds studied have been reported in detail.[15,16] The ultraviolet absorption spectra were determined with a Beckman DU spectrophotometer using the technique described previously.[18]

Acknowledgment.—The assistance of Mrs. M. Becker is gratefully acknowledged.

(18) G. W. Ewing and E. A. Steck, THIS JOURNAL, **68**, 3181 (1946).

RENSSELAER, NEW YORK

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

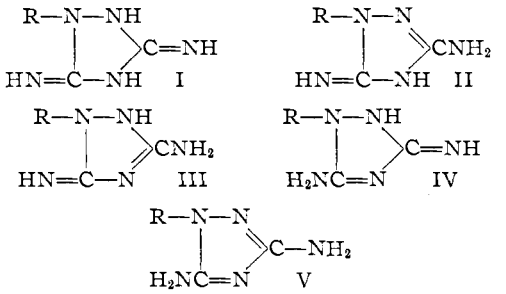
Absorption Spectra of Heterocycles. VIII.[1] Some Guanazole Derivatives

BY EDGAR A. STECK AND FREDERICK C. NACHOD

RECEIVED MARCH 9, 1957

The ultraviolet absorption spectra of several 1-arylguanazoles have been determined and their relation with structure treated. As a result of chemical and physical considerations, it has been suggested that 1-arylguanazoles be formulated as 3(5)-amino-1-aryl-5(3)-imino-1,2,4-triazolones (III) or (IV) rather than as 1-aryl-3,5-diimino-1,2,4-triazolidines (I).

The investigation of guanazole derivatives as potential pharmaceuticals[2] led to the preparation of certain 1-aryl-, 1-aryl-2-substituted and 1-aryl-3-substituted guanazoles which showed interesting structural aspects. Stollé and Dietrich[3] have noted that five structures (I-V) may be assigned to 1-substituted guanazoles, but no further treatment of this matter has been reported. The present discussion is based upon the ultraviolet absorption spectra of the 1-arylguanazoles and derivatives.



The reaction of arylhydrazines with cyanoguanidine might result in the formation of 1-arylguanazoles having several possible structures, as indicated by formulas I-V. These types represent the relationship of these 1,2,4-triazoles with guanidines and biguanides where arrangement of the atoms may be considered as being formed of two amidine groups. In these electrically neutral structures it is seen readily that the greatest degree of conjugation is present in V; forms III and IV show less conjugation, and no conjugation occurs in I and II. A study was made of the various proton donor and acceptor forms possible for those 1,2,4-triazole derivatives known as guanazoles; a summary of these considerations is shown in Table I. The contribution of the non-conjugated forms exceeds those of either conjugated type; this is in harmony with the experimental findings.

In Fig. 1 are shown the spectra of 1-phenylguanazole in acid, base and ethanol. For purposes of comparison, the spectrum of biphenyl in hexane[4] is also included since, as will be seen later in the case of 1-(4-xenyl)-guanazole (Fig. 3), there is a typical super-position of the component spectra in the solvent studied. It may be noted that the highest maximum in the spectrum of 1-phenylguanazole is attained in alcoholic solution. There is a related shift in the spectrum to longer wave lengths in neutral solution, whereas the spectra in solutions of both high and low *p*H are found to

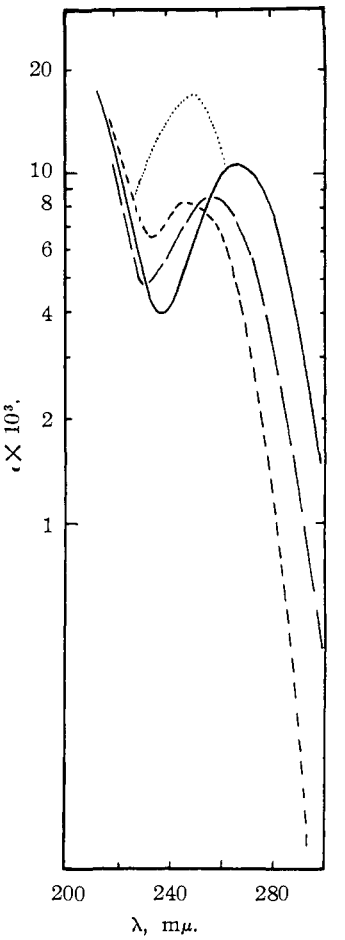


Fig. 1.—Absorption spectra of 5(3)-amino-3(5)-imino-1-phenyl-1,2,4-triazolone in: —, 95% ethanol; - - - , 0.01 *N* HCl; — —, 0.01 *N* NaOH; and . . . .biphenyl in *n*-hexane.

(1) Previous contributions, E. A. Steck and F. C. Nachod, THIS JOURNAL, **79**, 4408 (1957).

(2) E. A. Steck, R. P. Brundage and L. T. Fletcher, to be published.

(3) R. Stollé and W. Dietrich, *J. prakt. Chem.*, [2] **139**, 193 (1934).

(4) M. T. O'Shaughnessy and W. H. Rodebush, THIS JOURNAL, **62**, 2096 (1940).

occur at shorter wave lengths. This, too, is in agreement with our above-noted considerations. To test the idea further, it was decided to determine the influence of *p*H upon the extinction coefficients in the spectrum of 1-phenylguanazole. Figure 2 shows the results of spectral studies made with a number of buffer solutions. This demonstrates clearly that a maximum in conjugation, as may be attributable to forms III-V, results at neutral *p*H range. Moreover, it should be noted that the hyperchromic effect in ethanolic solution (Fig. 1) is to be ascribed to an additional solvent effect.

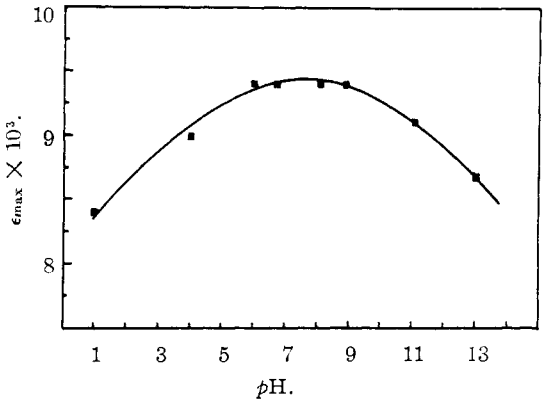


Fig. 2.—Change of extinction coefficients of maxima in the spectra of 5(3)-amino-3(5)imino-1-phenyl-1,2,4-triazolone buffer systems.

The spectra for 1-(4-xenyl)-guanazole in ethanol, acid and base are shown in Fig. 3. There are two maxima in the spectral curves determined with use of solutions in sodium hydroxide and ethanol; the relative positions of the curves are in the expected order and magnitude. In acid solution the maximum obtained for 1-(4-xenyl)-guanazole is to be seen to occur at the same wave length as for biphenyl in hexane solution[4] (Fig. 1), namely, 248 mμ. A characteristic curve with a single maximum is the result of the influence of the non-conjugated aromatic and heterocyclic contributors in 1-(4-xenyl)-guanazole.

Figure 4 shows the spectra for 1-(2-naphthyl)-guanazole in the three customary solvents. The pattern of these data obtained in acidic, basic and neutral solutions reflects the individual contributions of the aromatic and heterocyclic moieties in-

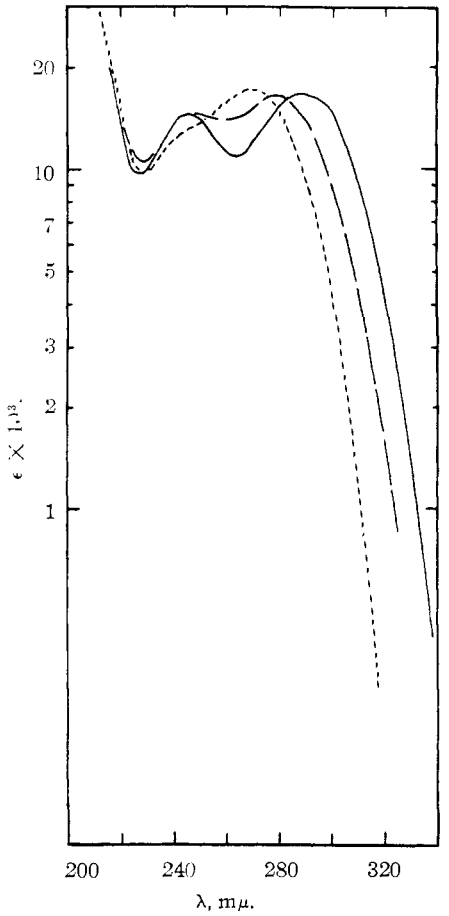


Fig. 3.—Absorption spectra of 5(3)amino-3(5)-imino-1-*p*-xenyl-1,2,3-triazolone in: —, 95% ethanol; - - - -, 0.01 *N* HCl; — —, 0.01 *N* NaOH.

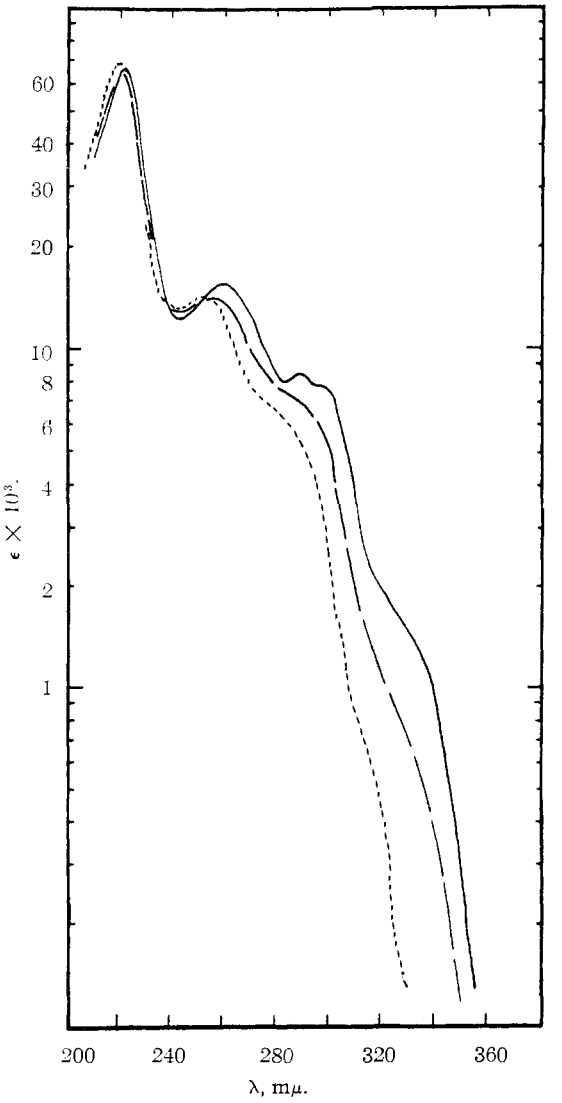


Fig. 4.—Absorption spectra of 5(3)-amino-3(5)-imino-1-β-naphthyl-1,2,4-triazolone in: — 95% ethanol; - - - - 0.01 *N* HCl; — — 0.01 *N* NaOH.

volved. The maxima contributed by the 1,2,4-triazole nucleus appear again in the 260 mμ region for the three solvents, while the naphthalenic substituent shows its strong and characteristic absorption in the 220 mμ region (for a comparison with the spectra of 2-naphthol and 2-naphthylamine, *cf.* refs. 5 and 6). In the case of the absorption spectrum obtained when ethanol was the solvent, there is to be seen the expected bathochromic shift with relation to the other two solvents. It is also to be noted that the characteristic triplet was maintained in the spectrum of 1-(2-naphthyl)-guanazole in alcohol but was nearly obliterated in acidic and alkaline solvents, only a memory of it remaining in the respective inflection points.

The influence of a para-halogen substituent upon the absorption spectrum of 1-phenylguanazole is indicated in Fig. 5. The expected batho- and hyperchromic shifts upon transition from the fluoro to the iodo grouping is indeed realized. It should be noted, however, that there is little change in character from 1-(4-chlorophenyl)-guanazole to the related bromo compound. The development of an additional maximum in the short wave region first appears in 1-(4-bromophenyl)-guanazole and is again evidenced with a concomitant bathochromic shift in the case of the spectrum of the iodo compound. These effects appear to be caused by the halogen substitution regardless of whether it is attached directly to an heterocyclic system (as in the case of certain quinolines),[7] or linked to the heterocyclic portion of a molecule *via* a phenyl group.

Table II gives the characteristics of the absorption spectra of five additional 1-arylguanazoles in ethanol, sodium hydroxide and hydrochloric acid solutions. A comparison of the salient features of the spectra of 1-(4-methylphenyl)-guanazole with the related types having 1-(3-chlorophenyl) and 1-(3-chloro-4-methylphenyl) groups shows that substitution of position 3 by a chloro group has less influence upon the spectrum of 1-(3-chloro-4-methylphenyl)-guanazole than does the 4-methyl group. This is presumably due to the interaction of position and inductive effects.[8] Also given in Table II are characteristic portions of the spectra of 1-[4-(4′-methylphenoxy)-phenyl]-guanazole and 1-[4-(4′-methylphenylthio)-phenyl]-guanazole, which may likewise be compared with 1-(4-methylphenyl)-guanazole. The interposition of the phenoxy group between the methyl and phenyl radicals results only in an intensification but not a shift in the respective spectra of 1-[4-(4′-methylphenoxy)-phenyl]-guanazole from those of the related 1-(4-methylphenyl) compound. However, the replacement of the oxygen by the heavier sulfur atom in 1-[4-(4′-methylphenylthio)-phenyl]-guanazole not only leads to further intensification but also to a bathochromic shift of *ca.* 21–25 mμ. This is to be expected, as the sulfur atom has a

(5) G. W. Ewing and E. A. Steck, THIS JOURNAL, **68**, 2164 (1946).
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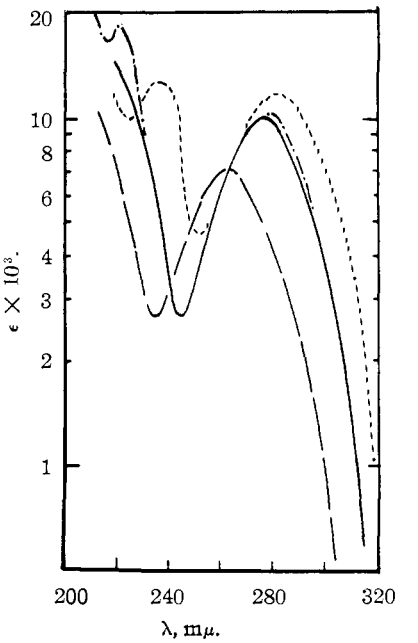

Fig. 5.—Absorption spectra in 95% ethanol of: —, 5(3)-amino-3(5)-imino-1-*p*-chlorophenyl-1,2,4-triazolone; — —, 5(3)-amino-3(5)-imino-1-*p*-fluorophenyl-1,2,4-triazolone; — · —, 5(3)-amino-3(5)-imino-1-*p*-bromophenyl-1,2,4-triazolone; - - - -, 5(3)-amino-3(5)-imino-1-*p*-iodophenyl-1,2,4-triazolone.

higher inherent resonance energy than the oxygen atom. McMurry[9] has reported data relating to this matter, and it has been further substantiated by several authors (*inter alia*, refs. 10–13).

TABLE I

CONTRIBUTORY EFFECTS OF IONIC CONFIGURATIONS IN 1-ARYLGUANAZOLE TYPES

Type of conjugation	Proton acceptor forms	Proton donor forms
Endocyclic	6	2
Endo-exo cyclic	6	3
Non-conjugated	11	7

TABLE II

SPECTRAL CHARACTERISTICS OF SOME 1-ARYLGUANAZOLES

	Maxima[a]; λ in mμ, ε × 10³					
	Ethanol		0.01 *N* HCl		0.01 *N* NaOH	
1-Arylguanazoles	λ	ε	λ	ε	λ	ε
1-(3-Chlorophenyl)	272	7.7	256	5.5	266	6.2
	(246	2.7)	(240	3.8)	(240	3.2)
1-(4-Methylphenyl)	267	9.1	248	7.8	256	8.0
	(239	3.4)	(256	6.0)	(232	4.4)
1-(3-Chloro-4-methylphenyl)	268	9.4	251	6.9	259	7.8
	(242	3.2)	(239	5.0)	(236	4.0)
1-[4-(4′-Methylphenoxy)-phenyl]	267	12.8[b]	248	12.2[b]	256	11.1[b]
	(245	8.5)	(240	12.0)	(243	10.2)
1-[4-(4′-Methylphenylthio)-phenyl]	288	16.1[b]	273	14.3[b]	280	14.8[b]
	(240	7.7)	(239	7.7)	(238	8.1)

[a] Values for minima are given in parentheses. [b] Flat maximum.

Table III shows a comparison of the spectra of 1-phenylguanazole with that of 2-methyl-1-phenyl-

(9) H. L. McMurry, *J. Chem. Phys.*, **9**, 241 (1941).
(10) R. N. Jones, THIS JOURNAL, **67**, 2127 (1945).
(11) R. O. Clinton and C. M. Suter, *ibid.*, **70**, 491 (1948).
(12) E. A. Fehnel and M. Carmack, *ibid.*, **71**, 84, 2889 (1949).
(13) R. B. Hannan, J. H. Lieblich and A. G. Renfrew, *ibid.*, **71**, 3733 (1949).

guanazole. The 2-methyl group obliterates not only the effects based upon tautomerism in the 1-phenylguanazole but, presumably, also that of some of the ionic contributions. As a consequence, the original pattern is really lost, and a faint memory is apparent only at the inflection points.

The 1-aryl-3,5-diimino-1,2,4-triazolidine structure (*i.e.*, I) for the 1-arylguanazoles has been preferred by Pellizzari.[14] This diimino formula does not readily explain the loss of only one nitrogen atom when 1-phenylguanazole is treated with caustic[15] and the behavior on acetylation.[15] The formation of monohydrochlorides and picrates[14,15] by the 1-arylguanazoles may not necessarily be considered in this matter, for it is well known that the mutual proximity of potentially basic groups may prevent the full showing of the basic properties. As examples of this behavior, one may cite certain polynitrogen heterocycles which form only monosalts.[16–18] Mann and Watson[19] have discussed salt formation in polyamine types, and they comment, *inter alia*, "it is suggested that the positive pole created by the initial salt formation exerts a strong electronic attraction, and this attraction, relayed by the inductive or mesomeric effect, may virtually immobilize the lone pair of electrons on a neighboring nitrogen atom and so deactivate this atom." Evidence here presented renders it desirable that the 1-substituted guanazoles should be considered to have the amino-imino structures indicated as III or IV rather than as diimino compounds as I. It does not appear to be possible to exclude the possibility of structure V, use of which has been made in the formulation of the products obtained from 1-phenylguanazole and isothiocyanates.[20]

(14) G. Pellizzari, *Gazz. chim. ital.*, **21**, II, 14 (1891); **24**, I, 481 (1894).
(15) G. Pellizzari and C. Roncagliolo, *ibid.*, 31, I, 477 (1901).
(16) C. Stoehr, *J. prakt. Chem.*, [2] **51**, 456, 462 (1895).
(17) O. Hinsberg, *Ann.*, **237**, 335 (1887); **292**, 245 (1896).
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(19) F. G. Mann and J. Watson, *J. Org. Chem.*, **13**, 502 (1948).

TABLE III
SPECTRAL CHARACTERISTICS OF SOME GUANAZOLE DERIVATIVES

Guanazole derivatives	Maxima[a]; λ in mμ, ε × 10³ — Ethanol λ	ε	0.01 *N* HCl λ	ε	0.01 *N* NaOH λ	ε
1-Phenyl	266	10.6	250	8.4	254	8.9
	(238	4.0)	(237	6.6)	(232	5.1)
2-Methyl-1-phenyl	216	30.0	224	19.7	220	22.1[b]
	245	7.0[b]	(218	18.1)	260	6.1[b]

[a] Values for minima given in parentheses. [b] Inflection point.

Experimental

1-Arylguanazoles.—All guanazoles were prepared as described in another publication.[2]

Absorption Spectra.—The spectrophotometric studies were all carried out with a Beckman quartz spectrophotometer, model DU, serial no. D-377. The method and solvents used have been described in other contributions from these laboratories.[5,6]

Acknowledgments.—To Dr. E. J. Lawson we owe much for his helpful counsel and patience in discussions concerning the potential ionic configurations in 1-arylguanazoles. A considerable portion of the spectrophotometric studies have been due to the efforts of Mrs. M. Becker and Mr. M. Priznar.

(20) E. Fromm and R. Kapeller-Adler, *Ann.*, **467**, 248, 267 (1928).

RENSSELAER, N. Y.

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Some 9-Amino-3-nitroacridine Derivatives

BY EDGAR A. STECK, JOHANNES S. BUCK[1] AND LYNN T. FLETCHER

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A series of 9-amino-3-nitroacridine types bearing hydroxylated side-chains was prepared for investigation as potential chemotherapeutic agents. In most cases, the 6,7-positions of the acridine nucleus were substituted, as by dimethoxy, methylenedioxy and ethylenedioxy groups; two derivatives of 9-amino-7-butoxy-3-nitroacridine also were made.

It appears that the investigation of 9-amino-3-nitroacridine derivatives has been largely neglected because little antimalarial activity has been found in this type[2]; the most interesting property in the group lies in their activity against microörganisms, which is even exhibited by 9-amino-3-nitroacridine itself.[3–6a] 9-(3-Diethylamino-2-hydroxypropylamino)-6,7-dimethoxy-3-nitroacridine (I), also known as Nitroakridine 3582 (Hoeschst) and 3043B for Entozon (Entozon is a mixture of I with 6,9-diamino-2-ethoxyacridine, Rivanol, and urea), and its salts have been the most carefully studied of the 9-amino-3-nitroacridines.[1,6–11] It has been claimed that this compound, and certain salts and combinations containing it, possess activity against

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(3) A. Albert, S. D. Rubbo, R. J. Goldacre, M. E. Davey and J. D. Stone, *Brit. J. Exptl. Pathol.*, **26**, 160 (1945).
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(7) C. S. Miller and C. A. Wagner, *J. Org. Chem.*, **13**, 891 (1948).
(8) British Intelligence Objectives Subcommittee (BIOS), Final Report 766, Items 22 and 24, London, England, 1946. Report by T. Dewing, W. J. C. Dyke, C. C. Green, Hindley, Hoblyn, G. E. H. Skrimshire and Wilkinson, p 11.
(9) M. Bockmühl and A. Fehrle. U. S. Patent 2,040,070; German Patent 608,668.
(10) P. E. C. Goissedet and R. L. Depois, U. S. Patent 2,092,114.
(11) K. Streitwolf and H. Oesterlin, German Patents, 613,349; 618,567.