Imidazoles. II. 5(or 4)-(Monosubstituted Triazeno)imidazole-4(or 5)-carboxamides[1]

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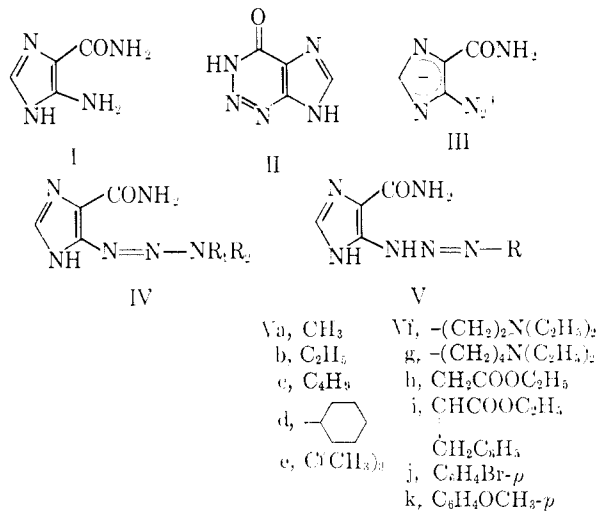
5(or 4)-(Monosubstituted triazeno)imidazole-4(or 5)-carboxamides (V or tautomeric structures) were synthesized by the reaction of 5-diazoimidazole-4-carboxamide with primary aliphatic and aromatic amines. The simpler alkyltriazeno derivatives were shown to decompose to 5(or 4)-aminoimidazole-4(or 5)-carboxamide (AIC) in aqueous or methanol solutions; they may, therefore, function as latent diazo compounds in which AIC is a carrier molecule. Triazenes obtained from two arylamines, ethyl glycinate, and ethyl phenylalanate decompose more slowly, and the mode of decomposition may be more complex. 5(or 4)-(Methyltriazeno)imidazole-4(or 5)-carboxamide is active against mouse leukemia L1210. Moderate activity was also observed among a few other derivatives in tests for antineoplastic effects.

Diazotization of 5(or 4)-aminoimidazole-4(or 5)-carboxamide (I) originally gave a compound described as 2-azahypoxanthine (imidazo[4,5-*d*]-*v*-triazin-4(3H)-one, II).[2] Subsequently, it was shown[3] that the diazotization may be performed in such a way that 5-diazoimidazole-4-carboxamide (III) may be isolated and characterized, even though it cyclizes readily in solution to 2-azahypoxanthine (II). The diazo derivative couples with aromatic substrates under conditions typical of diazonium coupling reactions.[4] Furthermore, reactions of III with secondary amines produce triazenes (IV), some of which have been shown to exert antitumor effects.[5] These results led to a study of the preparation and properties of some analogous 5(or 4)-(monosubstituted triazeno)imidazole-4(or 5)-carboxamides (V or tautomeric structures).



The simpler 5(or 4)-(monosubstituted triazeno)-imidazole-4(or 5)-carboxamides were initially obtained by procedures[4] used to prepare the disubstituted triazenoimidazoles. Reactions of III with the appropriate amines were allowed to proceed in anhydrous methanol or in an excess of the amine; yields were variable. After the instability of these triazenes in methanol had been demonstrated, as described below, ethyl acetate was employed as the solvent, and the pure triazenes V separated in high and reproducible yields. All reaction mixtures were routinely protected from light.

Disubstituted-triazeno derivatives (IV) have been shown previously to be stable (for at least 1–2 days) in aqueous solutions protected from light.[4] In solutions exposed to light, they were transformed into 2-azahypoxanthine (II), presumably *via* the diazo compound III. Ultraviolet absorption studies showed that the monoalkyl triazenes are unstable in solution even in the absence of light. In the example illustrated by Figure 1, maxima at 320 and 232 mμ (curve 1) ob-

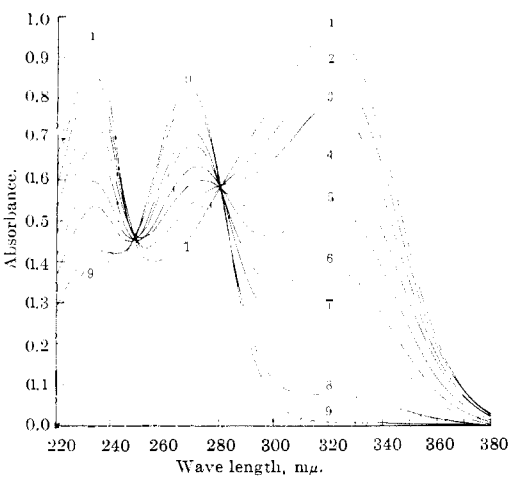


Figure 1.—Decomposition of 5(or 4)-(butyltriazeno)imidazole-4(or 5)-carboxamide (Ve) to 5(or 4)-aminoimidazole-4(or 5)-carboxamide (I) in methanol (7.36×10^{-5} *M*) at 25°. Time intervals in minutes between the addition of methanol and the beginning of the tracing of curves 1–9 were as follows: 2.5, 7.5, 12.5, 21.5, 30, 45, 60, 120, 240.

served within a few minutes of the addition of methanol to the butyltriazene (Ve) decreased in intensity even though the stock solution was protected from light in the same manner that solutions of the disubstituted triazenoimidazoles had been. The product resulting from dissociation of the butyltriazeno derivative, however, is not 2-azahypoxanthine, but AIC (I). Curve 9 arising from an increase in absorption at 268 mμ concomitant with the decrease of the initial maxima

(1) This investigation was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. SA-43-ph-1740 and Ph-43-64-51, and by the C. F. Kettering Foundation.

(2) D. W. Wooley and E. Shaw, *J. Biol. Chem.* **189**, 401 (1951).

(3) Y. F. Shealy, R. F. Struck, L. B. Holum, and J. A. Montgomery, *J. Org. Chem.*, **26**, 2396 (1961).

(4) Y. F. Shealy, C. A. Krauth, and J. A. Montgomery, *ibid.*, **27**, 2150 (1962).

(5) Y. F. Shealy, J. A. Montgomery and W. R. Laster, Jr., *Biochem. Pharmacol.*, **11**, 674 (1962).

is identical, except for slight residual absorption in the 320-mμ region, with the spectrum of AIC free base in methanol. In like manner, it was shown that AIC is formed in either phosphate buffer (pH 7) or, more slowly, in methanol solutions of Va–c and in buffer solutions of Vf–g. The latter compounds were not studied in methanol. Isoabsorptive points were observed at 247–249 and at 280–282 mμ, unless the formation of AIC was essentially complete when the first spectra were recorded. The formation of AIC (I) from the monoalkyltriazenes was confirmed by isolation. A specimen, isolated following the dissociation of the butyltriazene in water, was shown by its melting point, infrared spectrum, and paper chromatographic behavior to be identical with authentic AIC free base.

Since the absorbance of pure AIC free base in methanol or buffer is zero above 315 mμ, the rate of disappearance of the simple triazenes may be estimated from the rate of disappearance of the absorption maximum in this region. The straight-line plot (Figure 2) of the logarithm of the absorbance at 320 mμ *vs.* time shows that the decomposition of the butyltriazene (Vc) follows first-order kinetics. In methanol, the half-life ($t_{0.5}$) of the butyltriazene at 25° was determined from Figure 2 to be 32 min.; in phosphate

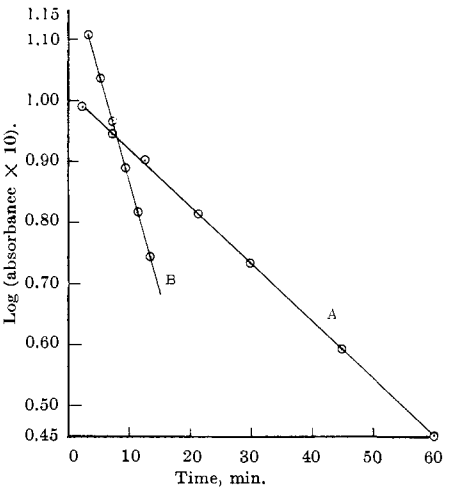


Figure 2.—First-order decomposition of Va and Vb to I at 25°. A, Vc (7.36×10^{-5} *M*) in methanol, absorbance at λ_{max} 320 mμ; B, Va (13.6×10^{-5} *M*) in phosphate buffer (pH 7), absorbance at λ_{max} 320 mμ.

buffer at pH 7, $t_{0.5}$ of the methyltriazene (Va) was similarly determined to be 8 min. Other observations of the dissociation of Va–c in methanol or buffer solutions were made at uncontrolled laboratory temperatures (near 25°) and give, therefore, only rough approximations of $t_{0.5}$; the differences were sufficiently great to permit qualitative comparisons. Thus, in methanol the approximate half-life values observed in this way for Va and Vb were 8 and 1 hr., respectively; in buffer, Vb and Vc had been converted almost completely to AIC when the first curves were traced at 7 and 2 min.,[6] respectively. The cyclohexyl (Vd) and *t*-butyl (Ve) derivatives proved to be less stable than the straight-chain alkyl derivatives. A specimen of Vd was obtained, but it decomposed on standing in the solid state. Addition of the diazoimidazole (III) to a solution of *t*-butylamine caused the evolution of a gas, which was assumed to be nitrogen, and 2-butene formed by immediate decomposition of the *t*-butyltriazeno derivative (Ve); AIC was demonstrated by paper chromatography to be present in the crude residue from the reaction.

Three additional structural variants (Vf and g, Vh and i, and Vj and k) were prepared, and their stability and biological activity were investigated. Basic groups were introduced into the triazene moiety as a possible means of stabilizing the triazene grouping. The diethylaminoethyltriazene (Vf) was, indeed, more stable than the simple alkyltriazenes, its half-life in buffer solution at 25° being approximately 3 hr. Separating the basic group from the triazene group by four carbon atoms decreased the stability; Vg appeared to form AIC in buffer at least as rapidly as the methyltriazene (Va). Both the ethoxycarbonylmethyl (Vh,i) and the aryl derivatives (Vj,k) decomposed in buffer solution more slowly than the alkyltriazenes. The spectral changes were more complex than those of Va–c and Vf,g, and interpretation was further complicated by the presence of ultraviolet-absorbing aryl groups in Vi–k. However, it was apparent that the *p*-methoxyphenyl derivative (Vk) was more stable than the methyltriazene, that the rate of disappearance of the phenylalanate derivative (Vi) approximated that of the diethylaminoethyl derivative (Vf), that the glycinate derivative (Vh) was more stable than Vi, and that the *p*-bromophenyl derivative (Vj) was the most stable of the derivatives prepared. Maxima near 270 mμ, suggestive of AIC, eventually appeared in the spectra of solutions of the glycinate and aryl derivatives, but it has not been established whether AIC is a decomposition product of these triazenes at pH 7. Whereas the ethyl (Vb) and butyl (Vc) derivatives rapidly decomposed in 0.1 *N* sodium hydroxide to AIC (λ_{max} 277 mμ in base), Vh and i were converted immediately by 0.1 *N* sodium hydroxide into products having maxima at 254 and 262 mμ, respectively. In methanol, Vh and i displayed a very slow decrease in their absorption maxima during a period of several days, and a methanol solution of the *p*-bromophenyl derivative showed no change during an 8-day period in which the solution was protected from light only during the first day.

The stability of the product of III and *p*-bromoaniline suggested that it might be an azo compound formed by rearrangement of the initially formed triazene.[7] This possibility was eliminated by treating the *p*-bromophenyl derivative at pH 1.5 with N,N-dimethylaniline. The principal product obtained was 4-bromo-4′-(dimethylamino)azobenzene (VI), which was identified by comparison with an authentic specimen.[8] The *p*-bromobenzenediazonium ion necessary for the formation of the azo compound VI must have come from the *p*-bromophenyltriazene (Vj). Paper chromato-

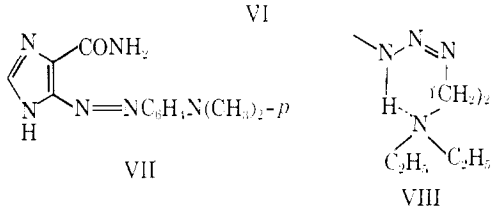
(6) These time intervals included periods of slower decomposition in methanol since the buffer solutions were prepared by first dissolving the specimens in methanol (because of their sparing solubility in water) and then diluting to the final concentrations with buffer.

(7) The preparation of 5(or 4)-amino-2-(*p*-bromophenylazo)imidazole-4(or 5)-carboxamide by coupling of AIC and *p*-bromobenzenediazonium chloride has been claimed: Y. Hirata, I. Teshima, and K. Iwashita, *Res. Rept. Nagoya Ind. Sci. Res. Inst.*, **No. 8**, 70 (1955); *Chem. Abstr.*, **51**, 5758i (1957).

(8) H. Goldschmidt and B. Bardach, *Ber.*, **25**, 1374 (1892); I. N. Zhmurova, *Zh. Obshch. Khim.*, **27**, 2704 (1957); *J. Gen. Chem. USSR*, **27**, 2747 (1957).

graphic evidence was obtained for the formation of a small amount of 5(or 4)-(*p*-dimethylaminophenylazo)-imidazole-4(or 5)-carboxamide[4] (VII), which would result from dissociation of Vj to III and *p*-bromoaniline. This experiment showed that the product isolated from the coupling of *III* and *p*-bromoaniline has the triazene structure (Vj) and that the principal mode of acid-catalyzed dissociation is the same as that of the alkyltriazeno derivatives.

AIC presumably forms by dissociation of the monoalkyltriazenes according to eq. 1, the rapid decomposition of RN_2^+ being the irreversible stage. The net result of the sequence of steps beginning with the reaction of a primary amine with the diazoimidazole (III) is a deamination of the amine *via* triazene formation.[9] The greater stability of the aryl derivatives may be due to the fact that the same mode of dissociation would produce aryldiazonium ions that, being more stable, could recouple and thereby establish equilibria between the triazenes and the dissociation products. The observations described above on the



$$V \rightarrow I + RN_2^+ \rightarrow N_2 + R^+ \rightarrow \text{etc.} \quad (1)$$

preparation of Vd,e and on the decomposition of Va–c in solution indicate that increasing the electron-donor properties of R of V, when R = simple alkyl groups, has a labilizing effect. Also, of the two derivatives within the groups Vh,i and Vj,k, the more stable derivative has the more electronegative R group. The diethylaminoethyl derivative (Vf), the most stable of the group Va–g, may owe its increased stability to intramolecular hydrogen bonding (VIII).

Biological.[10]—The studies on the decomposition of 5(or 4)-(monosubstituted triazeno)imidazole-4(or 5)-carboxamides showed that they are, in effect, latent diazo compounds and that considerable differences in the rate of dissociation of these triazenes can be effected by varying the substituent on the triazeno group. The chemotherapeutic significance of this finding is that, through the use of triazenes of type V, AIC might be employed as a carrier group for diazo compounds. Although the more unstable triazenes were expected to undergo some decomposition in the aqueous vehicle used to administer them[11] and in the aqueous environment *in vivo*, all were evaluated against leukemia L1210, Adenocarcinoma 755, and Sarcoma 180 in mice. Special precautions were taken in order to get as much as possible of the undissociated triazenes into the animals. Suspensions of the triazenes in a carboxymethylcellulose (CMC) vehicle (0.4% CMC and 0.85% NaCl) were injected within approximately 5 min. of the time that the solid triazenes came into contact with the CMC solution. In accordance with the protocol of the Cancer Chemotherapy National Service Center, toxic dosage levels were established for at least one tumor, usually S180, and these data were used to determine dose levels for the remaining tests. The test data tended to be somewhat erratic; for example, in three tests of Ve against Ca755 at 125 mg./kg./day the T/C values ranged from 23 to 110%. The explanation may lie in the fact that, despite precautions, slight differences in administering a compound may have caused considerable differences in the amount of the triazene that actually got into the animals. As shown in Table I, the methyltriazene (Va) is active against L1210 and Walker carcinoma 256 in rats. Other active tests were as follows: Vf gave a T/C value of 53% at 50 mg./kg./day and was toxic at 75 and at 100 mg./kg./day in tests *vs.* Ca755; Vh and Vj showed modest activity against Ca755 in preliminary tests; and Vb produced an increase in survival time of 140% of controls in one test, but only 114% in a second test, against L1210 at 187 mg./kg./day. None of the triazenes of type V prepared thus far have shown activity against S180.

TABLE I

5(OR 4)-(METHYLTRIAZENO)IMIDAZOLE-4(OR 5)-CARBOXAMIDE (Va) *vs.* ANIMAL TUMORS[a]

Tumor	Dose, mg./kg./day	Mortality	Av. wt. change, T/C[b]	Tumor data T/C[c]	T/C ratio, %
L1210	80	0/6	−3.8/−0.8	6.3/9.4	67
	60	0/6	−3.4/−0.8	7.3/9.4	77
	40	0/6	−2.0/−0.3	11.7/9.6	121
	30	0/6	−2.1/−0.1	16.5/9.3	177
	30	0/6	−1.5/+0.5	9.0/8.3	108
	30	0/6	−0.4/+1.3	16.0/8.7	183
	20	0/6	−2.5/+0.5	12.8/8.3	154
	15	0/6	−2.5/+0.5	12.8/8.3	154
	10	0/6	−1.6/+0.5	12.2/8.3	146
S180	100	5/6			
	50	2/6	−3.9/−0.1	685/1073	63
Ca755	40	0/10	+1.7/+1.4	1193/1055	113
Wa256	50	2/6	+17/+41	3.3/7.3	45

[a] T/C = treated animals/control animals. [b] Average weight change of host animals in milligrams for mice and in grams for rats. [c] Average tumor weights in milligrams for S180 and Ca755 and in grams for Wa256; average survival time in days for L1210.

Experimental Section[12]

5(or 4)-(Substituted Triazeno)imidazole-4(or 5)-carboxamides (Va–k).—The general procedure used to synthesize the triazenes Va–k is illustrated by the preparation of the 2-diethylaminoethyl derivative (Vf). During all operations involved in the preparation and purification of the triazenes, they were protected from light as much as possible by wrapping the reaction flasks, filter funnels, or other equipment used to contain the triazenes with aluminum foil. 5-Diazoimidazole-4-carboxamide (III) (400 mg., 2.9 mmoles) was added in small portions during 1.5 hr. to a well-stirred solution of 2.05 ml. (14.6 mmoles) of redistilled N,N-diethylethylenediamine in 10 ml. of dry ethyl acetate. The reaction mixture was kept under nitrogen and was protected from moisture. The mixture was stirred for an additional hour, and the precipitated product was collected on a filter, washed well with ethyl acetate, and dried in a high vacuum

(9) E. H. White and H. Scherrer, *Tetrahedron Letters*, **No. 21**, 758 (1961).

(10) Biological testing was performed by the Chemotherapy Department of Southern Research Institute under the auspices of the Cancer Chemotherapy National Service Center and under the supervision of Drs. F. M. Schabel, Jr., and W. R. Laster, Jr.

(11) During this *in vitro* period the triazenes were in suspension rather than completely in solution. Decomposition should have been less than might otherwise be expected.

(12) Solvent systems used to develop paper chromatograms were: (1) 1-butanol saturated with water, (2) 1-butanol–acetic acid–water (5:2:3 by volume), (3) 2-propanol–water–concentrated aqueous ammonia (70:25:5 by volume), and (4) acetate buffer (pH 6.1 or 6.7). Spots were detected with ultraviolet light at 254 and 365 mμ.

TABLE II: 5(OR 4)-(MONOSUBSTITUTED TRIAZENO)IMIDAZOLE-4(OR 5)-CARBOXAMIDES

Compd. No.	R	Amine, equiv.	Solvent,[a] ml./g. of III	Reaction time, hr.[b,c]	Yield, %	Approx.[d] decomp. temp., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	λ_{max}, mμ ($\epsilon \times 10^{-3}$)	Solvent[e]
Va	CH_3	25	25	0.75 + 2[f]	89	175–180	$C_5H_8N_6O$	35.71	4.80	49.98	35.99	5.10	49.62	231, 315[g]	A
Vb	C_2H_5	36	25	1.5 + 1[f]	94	154–158	$C_6H_{10}N_6O$	39.55	5.53	46.13	39.49	5.60	46.14	232, 319	A
Vc	C_4H_9		25[h]	0.5 + 2	86	150–155	$C_8H_{14}N_6O$	45.70	6.71	39.98	45.86	6.62	39.71	232, 320	A
Vd	C_6H_{11}		25[h]	1.5 + 1	42[i]		$C_{16}H_{29}N_7O$[j]	57.28	8.72	29.23	56.84	8.66	29.36		
Ve	$(CH_3)_2C$	10	25	1.5[f]											
Vf	$(CH_2)_2$-$N(C_2H_5)_2$	5	25	1.5 + 1	94	150–153	$C_{10}H_{19}N_7O$	47.43	7.56	38.73	47.48	7.55	38.63	232, 324	B
Vg	$(CH_2)_4$-$N(C_2H_5)_2$	5	25	1 + 1.5	86	155–160	$C_{12}H_{23}N_7O$	51.24	8.24	34.87	51.22	8.49	34.77		
Vh	$CH_2COOC_2H_5$	10	100	0.5 + 5	97	215–218	$C_8H_{12}N_6O_3$	40.00	5.04	34.99	40.08	4.99	34.74	316[k]	A
														318[k]	B
Vi	$C_2H_5OOCCHCH_2C_6H_5$	5	250	0.5 + 3.5	90	180–185	$C_{15}H_{18}N_6O_3$	54.54	5.49	25.44	54.74	5.51	25.14	322[k]	B
Vj	p-BrC_6H_4	5	37.5[f]	1 + 18	39	208–210	$C_9H_9BrN_6O$[m]	38.85	2.94	27.19	38.58	3.10	26.80	233 (13.3), 296 (5.3), 305 (5.4), 377 (28.5)	B
Vk	p-$CH_3OC_6H_4$	10	50	0.5 + 18	95	185–190	$C_{11}H_{12}N_6O_2$	50.76	4.65	32.29	50.98	4.75	32.24		

[a] Ethyl acetate unless otherwise specified. [b] III was added during the period given by the first number. The mixture was then stirred during the period given by the second number. [c] Reaction at room temperature unless otherwise specified. [d] All of these derivatives decomposed explosively when sprinkled along the gradiently heated bar of a Kofler Heizbank melting point apparatus. The temperature at which explosive decomposition occurred almost immediately was recorded. [e] A = methanol, B = phosphate buffer (pH 7). [f] The preparation of the ethyl acetate solution of the amine and the reaction with III were conducted at 0–5°. [g] 320 mμ in B. [h] Excess amine as solvent. [i] As cyclohexylamine salt. Analyses were performed on the same day the reaction was performed. An earlier sample decomposed within 4 days. Evolution of gas was observed during some attempts to prepare Vd. [j] Decomposition with evolution of gas during slow addition of III; stirred additional 1.5 hr; AIC (I) detected chromatographically in crude product. [k] Spectrum not recorded below 245 mμ because of presence of small amount of dimethyl sulfoxide used to dissolve sample. [l] Methanol. [m] *Anal.* Calcd.: Br, 25.85. Found: Br, 25.53.

at room temperature over P_2O_5; yield, 694 mg. (94%). A larger amount of Vf that, according to its infrared spectrum, contained a small amount of the diazo starting material was purified by slurrying 5–10 min. with water at pH 9, washing with water, and drying rapidly; yield, 80%.

Data on the preparation and characterization of the individual triazenes are recorded in Table II. Because of the instability of the triazenes, purification procedures, other than washing or slurrying the crude products with ethyl acetate or with ether, were usually not practicable. An exception, in addition to Vf, was the *p*-bromophenyl derivative (Vj), which was recrystallized from 2-methoxyethanol by the addition of a mixture of benzene and hexane. Generally, however, the preparative procedure was designed to cause precipitation of the triazene in analytically pure form. All of the triazenes are stored in brown bottles over a drying agent. Although they appear to be stable at room temperature when stored in this manner, they are routinely kept at 0–5°.

5(or 4)-Aminoimidazole-4(or 5)-carboxamide (I) from 5(or 4)-(Butyltriazeno)imidazole-4(or 5)-carboxamide (Vc).—A suspension of 200 mg. of Vc in 15 ml. of water was stirred at room temperature. A gas, presumed to be nitrogen, was evolved, and the mixture became homogeneous within 1.5 hr. The ultraviolet spectrum of an aliquot indicated that only AIC (I) was present. Lyophilization of the reaction solution left 144 mg. of product (theoretical yield of AIC monohydrate, 138 mg.). Recrystallization of 100 mg. of this material from water and drying of the recrystallized product *in vacuo* over P_2O_5 at room temperature gave 58 mg. (adjusted yield, 60%) of crystals melting at 172–174° dec. (capillary), lit.[13] 170–171°. The infrared spectrum was identical with that of authentic AIC monohydrate, and paper chromatograms showed only AIC.

Acidic Dissociation of 5(or 4)-(*p*-Bromophenyltriazeno)imidazole-4(or 5)-carboxamide (Vj).—A mixture of 400 mg. of Vj, 3.3 ml. of N,N-dimethylaniline, 20 ml. of ethanol, and 20 ml. of water was acidified to pH 1.5 with concentrated HCl and stirred at room temperature for 42 hr. A red precipitate was collected by filtration, washed with water, and dried; 316 mg. (80% calcd. as VI). Paper chromatography showed that this material was chiefly 4-bromo-4′-(dimethylamino)azobenzene containing small amounts of two impurities. Paper chromatograms of the filtrate were complex, containing several spots one of which was VI. Recrystallization of the red solid from ethanol gave 180 mg. (46%) of red crystals, m.p. 159–160°. The infrared spectrum and paper chromatograms of this material were identical with those of an authentic specimen of VI (m.p. 159–160°) prepared by coupling *p*-bromobenzenediazonium chloride with N,N-dimethylaniline.[8] Paper chromatograms of a second crop (60 mg.) contained spots corresponding to VI, the starting material Vj, and 5(or 4)-(*p*-dimethylaminophenylazo)imidazole-4(or 5)-carboxamide[4] (VII). The latter compound is the expected product if dissociation of Vj gives the diazoimidazole III and *p*-bromoaniline.

Ultraviolet spectra were recorded with a Cary Model 14 recording spectrophotometer. Solutions of the triazenes were prepared by rapidly dissolving a weighed specimen in 5–10 ml. of methanol and quickly diluting to the final concentration of about 10 mg./l. with either methanol or pH 7 phosphate buffer except for Vh and i, which had to be dissolved initially in a small quantity of dimethyl sulfoxide before the final dilutions were made. The time (t) was recorded when a tracing was begun at 400 mμ; about 80 sec. elapsed between the beginning at 400 mμ and the recording of maxima near 320 mμ. Solutions were protected from light during their preparation, and stock solutions were stored in the dark either at uncontrolled room temperature (near 25°) or, where stated, at 25° (thermostated bath). During studies on the decomposition of a triazene, a fresh portion of the stock solution was rapidly transferred to the cuvette for the tracing of each curve at a given time. In addition, observance of the dissociation of the methyltriazene (Va) and diethylaminoethyltriazene (Vf) derivatives in phosphate buffer was repeated with a Perkin-Elmer Model 202 spectrophotometer; the triazene solution was left continuously in the thermostated (25°) cuvette, readings were made at the long wave-length maximum, and the solution was shielded from the light beam between readings. The half-life values were in agreement with those found by the method described above.

(13) J. A. Montgomery, K. Hewson, R. F. Struck, and Y. F. Shealy, *J. Org. Chem.*, **24**, 256 (1959).

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Synthesis and Pharmacological Properties of 1-Substituted 3-Dimethylaminoalkoxy-1H-indazoles

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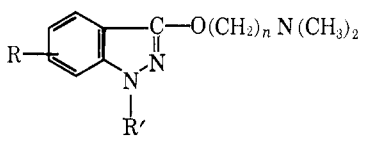
Thirty-four 1-substituted 3-dimethylaminoalkoxy-1H-indazoles have been synthesized and pharmacologically evaluated. Some of them proved to be interesting analgesic, antiinflammatory, and antispasmodic agents of low toxicity.

In our search for new structures with antiinflammatory activities it was considered of interest to synthesize a series having the general formula I. Very little is



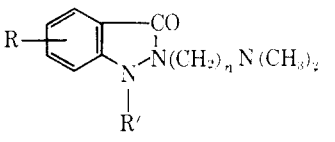
I

R = H, Cl; R′ = alkyl, aryl, or arylalkyl; n = 2, 3

known about the pharmacology of indazole derivatives, although the structural analogies with some classes of biologically active substances, such as serotonin and antihistaminic drugs, are apparent.

The first step in the synthesis was to perfect a method for the preparation of 3-hydroxy-1H-indazoles. For this purpose we made use of the pyrolysis of carbamoyl azides. Many of these substances had not yet been described, but they were easily obtained from the corresponding anilines through the carbamoyl chlorides and subsequent reaction with sodium azide. As it has been previously pointed out for certain benzyl derivatives,[1] pyrolysis of azides leads almost always to the simultaneous formation of 3-hydroxy-1H-indazoles and benzimidazolin-2-ones. Nevertheless, this does not represent an obstacle to the preparative method, since the reaction products can be easily separated by their differing acidity. In three other cases we carried out a reduction of N-nitrosoanthranilic acids with sodium hydrosulfite following a procedure previously described.[1]

The 3-hydroxy-1H-indazoles were transformed to the corresponding sodium salts and allowed to react in inert solvents with the proper chloroalkyldialkylamines, using different bases, solvents, ratios of reacting substances, temperatures, and periods of heating. Through all these varying conditions, the formation of the derivatives of type I was always accompanied by side products. Only in a few cases were these isolated and identified; generally, we limited ourselves to separating compounds I from the mixtures. This could be easily accomplished by chromatography (see Experimental Section). These substances are the lactamic compounds (II) as pointed out in specific cases by Schmutz, *et al.*[2] We isolated compounds of type II



II

only on two occasions, since we were interested in the pharmacological investigation of the isomers of two given compounds of our series (R′ = C_6H_5, n = 2; and R′ = $C_6H_5CH_2$, n = 3). Nevertheless, infrared spectra showed their presence in most cases. These spectra contain a carbonyl band (the most intense of each spectrum) around 1700 cm.$^{-1}$ and lack the C=N band around 1525 cm.$^{-1}$, characteristic of the compounds of formula I. The differences in the other regions of the spectra are less pronounced (Figure 1).

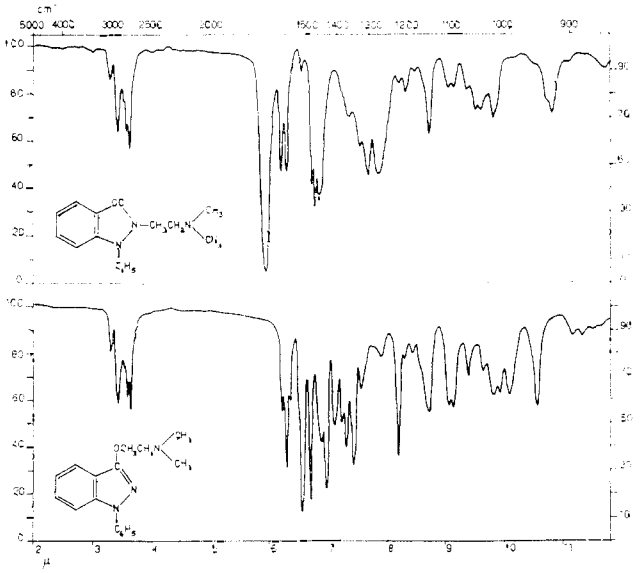


Figure 1.—Infrared spectra of 2-β-dimethylaminoethyl-1-phenylindazolin-3-one and of 3-β-dimethylaminoethoxy-1-phenyl-1H-indazole determined in CCl_4.

(1) L. Baiocchi, G. Corsi, and G. Palazzo, *Ann. Chim.* (Rome), **55**, 116 (1965).

(2) J. Schmutz, F. Hunziger, and W. Michaelis, *Helv. Chim. Acta*, **47**, 1986 (1964).