SECTION B
Physical Organic Chemistry

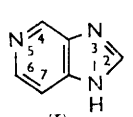
Ionisation Constants of Heterocyclic Substances. Part VIII.[1] 1,3,5-Triazaindenes

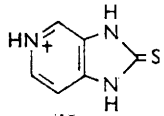
By G. B. Barlin

Syntheses are described for seven new chloro-, hydroxy-, mercapto-, and methylthio-1,3,5-triazaindenes with these substituents in the 2-, 6-, and 2,6-positions, and also for their methyl derivatives. Methylation of 2-methylthio-1,3,5-triazaindene gives a mixture of the *N*-1, *N*-3, and *N*-5 monomethyl derivatives, the structures of which are established by unambiguous syntheses. 6-Chloro-1,3,5-triazaindene similarly gives three products, two of which have been identified as the *N*-1 and *N*-3 monomethyl derivatives. The effects of substituents and the position of protonation on the ionisation constants and ultraviolet spectra are discussed.

1,3,5-TRIAZAINDENES (I) are of importance because the nucleus occurs in the streptothricin family of antibiotics.[2] In addition, their methylated aza-derivatives (*N*-methylpurines) such as 1-methylhypoxanthine and 1-methyladenine have recently been isolated from human urine and ribonucleic acids, respectively,[3] and still others possess antitumour activity.[4]

1,3,5-Triazaindenes with substituents (chloro-, hydroxy-, mercapto-, and methylthio-) in the 2- and 6- and 2,6-positions have now been prepared from 3,4-diaminopyridine and 3,4-diamino-6-chloropyridine.[5] Also, methylations of 2-methylthio- and 6-chloro-1,3,5-triazaindene have been investigated.


(I)


(II)

2-Methylthio- and 6-chloro-1,3,5-triazaindene gave three derivatives, and the orientation of the products was established by unambiguous syntheses in five of the six examples. The three *N*-methyl-2-methylthio-1,3,5-triazaindenes were synthesised from the corresponding *N*-methyldiaminopyridines, as follows. 3-Amino-4-methylaminopyridine [6] and carbon disulphide in pyridine gave 2-mercapto-1-methyl-1,3,5-triazaindene which was methylated in cold aqueous alkali to give 1-methyl-2-methylthio-1,3,5-triazaindene. Similarly, 4-amino-3-methylaminopyridine [6] gave 3-methyl-2-methylthio-1,3,5-triazaindene. 5-Methyl-2-methylthio-1,3,5-triazaindene was prepared from 3,4-diaminopyridine through 3,4-diamino-1-methylpyridinium iodide and 2-mercapto-5-methyl-1,3,5-triazaindene.

6-Chloro-1(and 3)-methyl-1,3,5-triazaindenes were dechlorinated with hydrogen over palladium–charcoal–sodium acetate to the known 1-(and 3)-methyl-1,3,5-triazaindenes,[7] respectively (which had been synthesised from the relevant amino-methylaminopyridines). 6-Chloro-?-methyl-1,3,5-triazaindene (the " third isomer ") isolated from the methylation of 6-chloro-1,3,5-triazaindene could not be positively identified. 6-Chloro-5-methyl-1,3,5-triazaindene could not be synthesised from 4,5-diamino-2-chloro-1-methylpyridinium iodide and formic acid, formamide, or triethyl orthoformate–acetic anhydride, and 5-methyl-1,3,5-triazaindene could not be synthesised from 3,4-diamino-1-methylpyridinium iodide.

However, the " third isomer " was not 6-chloro-2-methyl-1,3,5-triazaindene (an authentic specimen of which was prepared), and the n.m.r. spectrum (see Table 1) is similar to that of 6-chloro-1-(and 3)-methyl-1,3,5-triazaindene.

Ultraviolet Spectra.—The ultraviolet spectra of the 1,3,5-triazaindenes are given in Table 2 (Figures 1—4 show further detail relevant to the discussion). Comparison of the neutral molecules of 1,3,5-triazaindene, 2-mercapto-, 2-methylthio-, and 6-chloro-1,3,5-triazaindene with their *N*-1, *N*-3, and *N*-5 methyl derivatives does not reveal conclusive evidence of a marked predominance of any one tautomeric form in the parent triazaindene, or in its 2-mercapto- (Figure 1) or 6-chloro-derivative. However, in 2-methylthio-1,3,5-triazaindene (Figure 2) it appears that the tautomer with

TABLE 1

N.m.r. spectra of 1,3,5-triazaindenes in DCl–D_2O

		τ values	
	Concn. DCl	H	CH_3
6-Cl	0·25N	0·53, 0·92, 1·95	—
6-Cl-1-Me	0·2N	0·70, 0·99, 1·89	5·85
6-Cl-3-Me	0·2N	0·43, 0·85, 1·94	5·69
6-Cl-?-Me	3N	0·40, 0·85, 1·48	5·48

[1] Part VII, G. B. Barlin, *J. Chem. Soc.*, 1965, 2260.
[2] E. E. van Tamelen, J. R. Dyer, H. A. Whaley, H. E. Carter, and G. B. Whitfield, *J. Amer. Chem. Soc.*, 1961, **83**, 4295.
[3] For references, see J. W. Jones and R. K. Robins, *J. Amer. Chem. Soc.*, 1962, **84**, 1914.
[4] C. W. Noel, D. W. Smith, and R. K. Robins, *J. Medicin. Pharmaceut. Chem.*, 1962, **5**, 996.
[5] A. Albert and G. B. Barlin, *J. Chem. Soc.*, 1963, 5156.
[6] J. W. Clark-Lewis and R. P. Singh, *J. Chem. Soc.*, 1962, 2379.
[7] Y. Mizuno, M. Ikehara, T. Itoh, and K. Saito, *J. Org. Chem.*, 1963, **28**, 1837.

TABLE 2

No.	Substance	Ionisation (H_2O; 20°) Species [a]	pK_a	Spread (±)	Concn. (M)	A.w.l. [b]	Spectroscopy in water [f, g] $\lambda_{max.}$(mμ)	log ε	pH [h]
1,3,5-*Triazaindene*									
1	Unsubst.	0					241, 247, 257, 262·5, 269, 273	3·58, 3·58, 3·56, 3·60, 3·54, 3·06	8·5
		+	6·10 [c]				*248*, 262, *267*	*3·57*, 3·64, *3·63*	4·0
		−	10·88 [c]				268, *274*	3·70, *3·65*	13·0
2	1-Me [d]	0					*251*, 256, 263, 270·5	*3·65*, 3·66, 3·64, 3·48	8·5
		+	6·17	0·05	0·00008	280	209, *255*, 263, *267*	4·67, *3·57*, 3·63, *3·61*	3·9
3	3-Me [e]	0					*245*, 250, *271*, 275, 283	*3·58*, 3·60, *3·66*, 3·71, 3·55	8·0
		+	5·77	0·04	0·00006	296	254, 284·5, *291*	3·68, 3·78, *3·72*	3·5
4	2-OH	0					*224*, 270, *275*, *286*	*3·88*, 3·75, *3·73*, *3·34*	8·12
		+	6·12	0·03	0·00004	250	215, *254*, 276	4·59, *3·58*, 3·88	3·9
		−	10·12	0·04	0·00004	250	255·5, 277, *280*	3·76, 3·86, *3·84*	12·4
		2−	>15				—	—	
5	2-SH	0					216, 243, *292*, 297, *315*	4·11, 4·30, *4·24*, 4·28, *3·81*	6·78
		+	4·93	0·04	0·00004	290	247, 314	4·46, 4·26	2·7
		−	8·63	0·03	0·00004	330	*224*, 230, *266*, 295·5 [g]	*4·33*, 4·34, *3·84*, 4·29	11·0
		2−	>14				—	—	
6	2-SH-1-Me	0					242·5, *291*, 298, *322*	4·33, *4·25*, 4·33, *3·41*	6·92
		+	5·03	0·02	0·00004	332	*231*, 249, 315·5	*3·96*, 4·51, 4·26	2·0
		−	8·81	0·05	0·00004	330	237, 296	4·44, 4·23	11·0
7	2-SH-3-Me	0					*226*, 242, *291*, 299, *320*	*4·15*, 4·32, *4·25*, 4·33, *3·70*	6·98
		+	5·05	0·03	0·00004	332	227, 249, 316	3·98, 4·51, 4·26	2·0
		−	8·92	0·05	0·00004	330	230, *276*, 298·5	4·43, *4·00*, 4·34	11·5
8	2-SH-5-Me	0					*237*, 250, 325	*4·19*, 4·36, 4·22	8·0
		+	5·24	0·03	0·00002	235	225, 250, *290*, 320	3·89, 4·49, *3·77*, 4·28	3·0
		−	10·80	0·04	0·00002	262	243, 253, 323	4·31, 4·32, 4·19	13·0
9	2-SMe	0					231, 287, *294*	4·33, 4·11, *4·07*	7·96
		+	5·98	0·03	0·00004	310	*226*, 236, 291	*4·29*, 4·40, 4·15	3·5
		−	9·95	0·04	0·00004	310	222, 283	4·54, 4·12	12·2
10	1-Me-2-SMe	0					219, 278, *284*	4·43, 4·03, *4·00*	9·0
		+	6·48	0·05	0·00003	300	238, 288·5	4·49, 3·99	4·0
11	3-Me-2-SMe	0					218, 267, *275*, 280·5, 288·5	4·38, 3·99, *4·02*, 4·06, 3·96	8·5
		+	6·28	0·05	0·00004	260	229, 294	4·24, 4·37	4·0
12	5-Me-2-SMe	0					238, 299	4·43, 4·23	9·0
		+	6·06	0·05	0·0001	249	238, 295	4·42, 4·17	2·0
13	4-Cl	0					*208*, 245, 250·5, *259*, 266, 273, *285*	*4·46*, 3·67, 3·69, *3·70*, 3·78, 3·71, *2·67*	6·0
		+	2·20	0·04	0·00004	280	*208*, 241, *250*, 270, *275*, *285*	*4·46*, 3·44, *3·48*, 3·79, *3·77*, *3·39*	0·0
		−	9·83	0·04	0·00004	280	212, *254*, *266*, *273*, 279, *286*	4·63, *3·55*, *3·70*, *3·75*, 3·76, 3·63	12·1
14	6-Cl	0					245, *252*, 272, 278, *288*	3·58, *3·53*, 3·55, 3·50, *3·00*	6·5
		+	2·70	0·04	0·00008	252	233, *241*, 274	3·56, *3·48*, 3·60	0·5
		−	10·19	0·03	0·00008	294	216, *256*, 276	4·62, *3·47*, 3·59	12·4
15	6-Cl-1-Me	0					210, 252, 257, 266, 272, *279*	4·66, 3·60, 3·62, 3·58, 3·59, *3·45*	5·0
		+	2·46	0·03	0·00008	289	*211*, *218*, 237, 242, *252*, 275, *282*	*4·55*, *4·24*, 3·49, 3·47, *3·39*, 3·60, *3·51*	0·46
		2+	−1·50	0·05	0·0004	290	—	—	
16	6-Cl-3-Me	0					210, 241, 249, 255, *277*, 284, *292*	4·63, 3·48, 3·50, 3·51, *3·58*, 3·63, *3·53*	5·0
		+	2·74	0·05	0·00008	294	236, *241*, *250*, 276, *283*, *300*	3·54, *3·51*, *3·34*, 3·62, *3·52*, *2·55*	0·5
		2+	−1·74	0·05	0·00008	294	211, *214*, *240*, 244, 283, *290*	4·59, *4·57*, *3·47*, 3·48, 3·69, *3·63*	−4·0
17	6-Cl-?-Me	0					226, 266, *273*, 301	4·65, 3·67, *3·62*, 3·52	9·0
		+	6·70	0·03	0·00006	310	215·5, *218*, 255, 282	4·74, *4·70*, 3·57, 3·58	4·50
		2+	−0·78	0·05	0·00006	260	211, 215, 241, 245, *254*, 282, *289*	4·69, 4·64, 3·55, 3·55, *3·26*, 3·69, *3·64*	−3·0
18	6-Cl-2-OH	0					210, 233, 278, *284*	4·67, 3·79, 3·70, *3·61*	6·0
		+	1·77	0·03	0·00008	294	224·5, 258, 285	4·70, 3·68, 3·77	−0·5
		−	9·48	0·02	0·00004	260	217·5, 260, 283, *289*	4·59, 3·83, 3·85, *3·80*	12·0
		2−	14·36	0·04	0·00005	305	—	—	
19	6-Cl-2-SH	0					217, 247, *296*, 304·5	4·12, 4·44, *4·32*, 4·41	4·3
		+	0·81	0·05	0·00004	340	230, 257·5, 324	3·90, 4·60, 4·23	−1·5
		−	7·76	0·05	0·00006	270	238, *274*, 304	4·43, *3·90*, 4·28	10·6
		2−	13·40	0·04	0·00008	330	241, 307	4·55, 4·22	14·5

TABLE 2 (*Continued*)

No.	Substance	Ionisation (H_2O; 20°) Species [a]	pK_a	Spread (±)	Concn. (M)	A.w.l. [b]	Spectroscopy in water [f, g] $\lambda_{max.}$ (mμ)	log ε	Ph [h]
20	6-Cl-2-SMe	0					227, 260, 286, *292*	4·49, 3·84, 4·08, *4·05*	5·5
		+	2·32	0·05	0·00004	312	243, 293	4·46, 4·12	0·0
		−	8·75	0·04	0·00004	305	229, 291, *299*	4·55, 4·08, *3·96*	11·0
21	2,6-Cl_2	0					210, *240*, 245, *251*, *268*, 273, 279·5, *287*	4·64, *3·67*, 3·70, *3·66*, *3·58*, 3·65, 3·60, *3·11*	4·0
		+	1·35	0·05	0·00005	290	217, *220*, 257, 281, *288*	4·73, *4·71*, 3·65, 3·65, *3·56*	−1·0
		−	6·85	0·04	0·00005	290	216·5, *256*, *270*, 274, *280*, 290	4·67, *3·55*, *3·70*, 3·71, *3·67*, 3·47	9·5
Pyridinium iodide									
22	3,4-$(NH_2)_2$-1-Me	0					—	—	
		+	>14 [j]				227·5, 294	4·30, 3·97	5·0
		2+	0·3	0·04	0·00001	268	267	4·24	−2·0
23	3,4-$(NH_2)_2$-2-Cl-1-Me	0					—	—	
		+	>14				*220*, 236, 295	*4·21*, 4·41, 3·93	5·0
		2+	−0·18	0·05	0·00001	268	220, *226*, 270	4·20, *4·09*, 4·34	−2·2

[a] 0 Neutral species, + cation, 2+ di-cation. − anion, 2− di-anion. [b] Analytical wavelength (mμ) for spectroscopic determinations of pK_a. [c] A. Albert and C. Pedersen, *J. Chem. Soc.*, 1956, 4683. [d] Y. Mizuno, M. Ikehara, T. Itoh, and K. Saito, *J. Org. Chem.*, 1963, **28**, 1837, give pK_a 6·10 and ultraviolet absorption spectra at pH 3·80, $\lambda_{max.}$ 253 mμ (ε 5000), 285 mμ (ε 6100); at pH 12·7, $\lambda_{max.}$ 249 mμ (ε 4300), 275 mμ (ε 5400). [e] Y. Mizuno, M. Ikehara, T. Itoh, and K. Saito, *J. Org. Chem.*, 1963, **28**, 1837, give pK_a 6·26—6·46, and ultraviolet absorption spectra at pH 1·26, $\lambda_{max.}$ 263 mμ (ε 4400); at pH 11·6, $\lambda_{max.}$ 255 mμ (ε 4800), 263 mμ (ε 4600). [f] For the spectra, reference solutions were compensated where required with potassium iodide. [g] Shoulders and inflections in italics. [h] pH values below 0 have been obtained in solutions of sulphuric acid to which Hammett acidity functions have been assigned. [i] J. W. Clark-Lewis and R. P. Singh, *J. Chem. Soc.*, 1962, 2379, give for a solution of pH 13·0, $\lambda_{max.}$ 232 mμ (ε 23,500), 298—299 mμ (ε 14,000). [j] See text.

hydrogen on N-5 is making a significant contribution. The absorption band in the 270—325 mμ region is seen to occur at shortest wavelength in the *N*-1 methyl

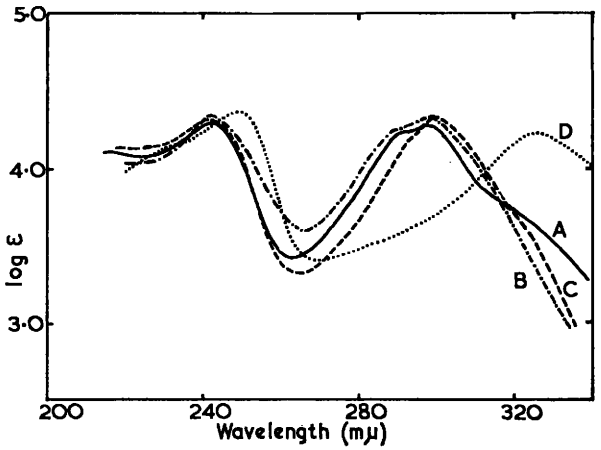


FIGURE 1 Ultraviolet spectra, in water at 20°, of neutral molecules of (A) 2-mercapto-1,3,5-triazaindene at pH 6·78; (B) 2-mercapto-1-methyl-1,3,5-triazaindene at pH 6·92; (C) 2-mercapto-3-methyl-1,3,5-triazaindene at pH 6·98; (D) 2-mercapto-5-methyl-1,3,5-triazaindene at pH 8·0

compounds and at longest wavelength in the *N*-5 methyl compounds. Similar effects have been noted in the purines [8] and triazaindenes.[7]

Replacement of the hydroxy-group by the mercapto-group (Nos. 5 and 19) produces a bathochromic shift, but methylation on sulphur (Nos. 9—12 and 20) brings about the usual pronounced hypsochromic shift.[9]

Examination of the spectra of the cations reveals qualitative evidence on the position of protonation. Thus, the cation of 6-chloro-1,3,5-triazaindene (Figure 3) closely resembles that of the *N*-1 and *N*-3 methyl derivatives but is quite different from that of the "third isomer." This indicates protonation of 6-chloro-1,3,5-triazaindene in the imidazole ring. However, in 2-methylthio-1,3,5-triazaindene (Figure 4) similar spectra are obtained for the parent and the *N*-1 and *N*-5 methyl derivatives (with some difference from the *N*-3 methyl compound), and protonation of 2-methylthio-1,3,5-triazaindene is believed to involve N-5 (see also the discussion of ionisation constants).

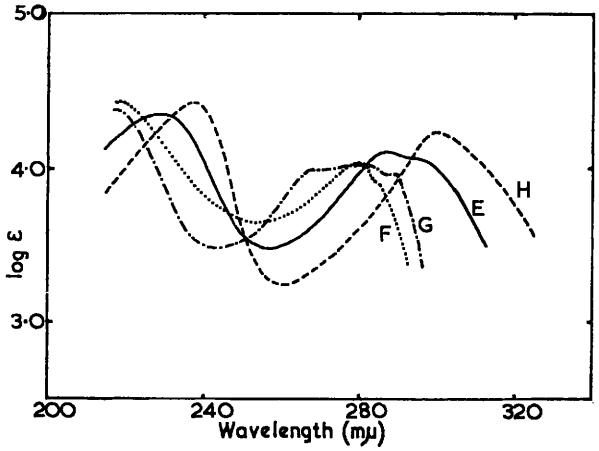


FIGURE 2 Ultraviolet spectra, in water at 20°, of neutral molecules of (E) 2-methylthio-1,3,5-triazaindene at pH 7·96; (F) 1-methyl-2-methylthio-1,3,5-triazaindene at pH 9·0; (G) 3-methyl-2-methylthio-1,3,5-triazaindene at pH 8·5; (H) 5-methyl-2-methylthio-1,3,5-triazaindene at pH 9·0

2-Mercapto-1,3,5-triazaindene is a special case; the spectrum of the cation is similar to that of the *N*-1,

[8] F. Bergmann, G. Levin, A. Kalmus, and H. Kwietny-Govrin, *J. Org. Chem.*, 1961, **26**, 1504.
[9] A. Albert and G. B. Barlin, *J. Chem. Soc.*, 1959, 2384; 1962, 3129.

N-3, and *N*-5 methyl derivatives, and this suggests that the predominant tautomer has a chromophoric system with hydrogen or methyl on each nitrogen atom (*e.g.*, II).

In the two nuclear *N*-methylpyridine compounds (Nos. 22 and 23) spectral changes on formation of the di-cations are exactly analogous to those observed in the diaminopyridines.[10]

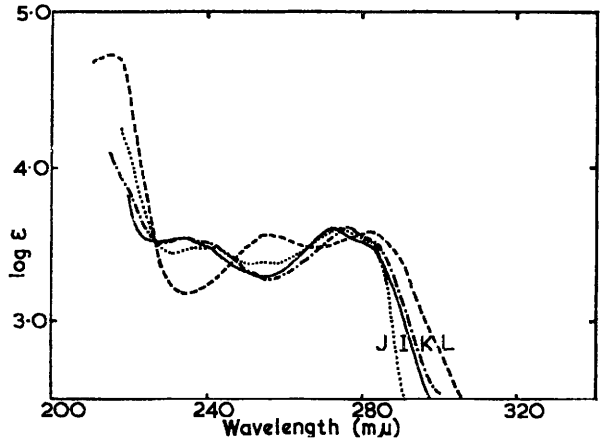


FIGURE 3 Ultraviolet spectra, in water at 20°, of mono-cations of (I) 6-chloro-1,3,5-triazaindene at pH 0·5; (J) 6-chloro-1-methyl-1,3,5-triazaindene at pH 0·46; (K) 6-chloro-3-methyl-1,3,5-triazaindene at pH 0·5; (L) 6-chloro-?-methyl-1,3,5-triazaindene at pH 4·5

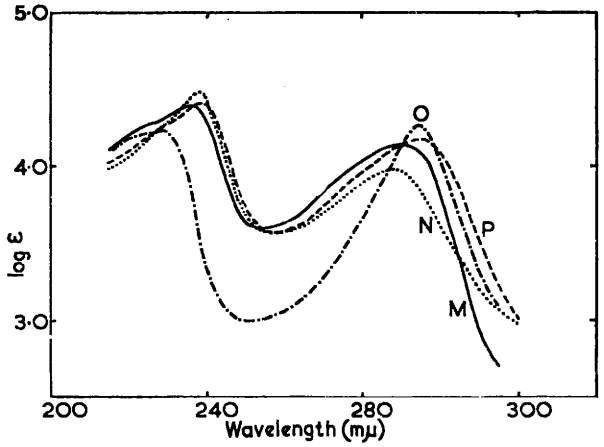


FIGURE 4 Ultraviolet spectra, in water at 20°, of mono-cations of (M) 2-methylthio-1,3,5-triazaindene at pH 3·5; (N) 1-methyl-2-methylthio-1,3,5-triazaindene at pH 4·0; (O) 3-methyl-2-methylthio-1,3,5-triazaindene at pH 4·0; (P) 5-methyl-2-methylthio-1,3,5-triazaindene at pH 2·0

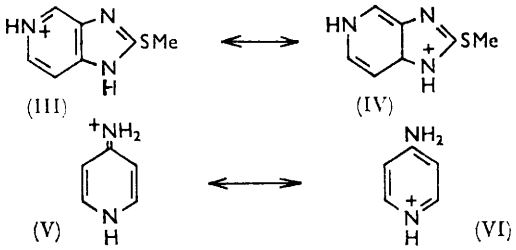
Ionisation Constants.—The ionisation constants are recorded in Table 2. The 1,3,5-triazaindenes, because they have only two doubly bound ring-nitrogen atoms, are stronger bases and weaker acids than the purines,[11,12] which have three. The exaltation of basic strength varies from 1·75 to 3·75 pH units and is most marked in the parent compound; similarly, the depression of acid strength varies from 1·88 to 2·28 units.

[10] G. B. Barlin, *J. Chem. Soc.*, 1964, 2150.
[11] A. Albert and D. J. Brown, *J. Chem. Soc.*, 1954, 2060.
[12] G. B. Barlin and N. B. Chapman, *J. Chem. Soc.*, 1965, 3017.

The effect on pK_a of substituents in 1,3,5-triazaindene is of the order found in the purines, except that a chlorine atom at the 4- or the 6-position has a considerably greater effect in the 1,3,5-triazaindene and the basic pK_a values are lowered by 3·9 and 3·4 units, respectively.

Table 2 shows that methylation on nitrogen in 1,3,5-triazaindene and its 2-mercapto-, 2-methylthio-, and 6-chloro-derivatives produces little effect on the basic pK_a values with the exception that the 6-chloro-?-methyl-1,3,5-triazaindene (No. 17, pK_a 6·70), isolated from the methylation of 6-chloro-1,3,5-triazaindene (pK_a 2·70), is a remarkably stronger base.

In 2-methylthio-1,3,5-triazaindene, protonation is believed to involve N-5 (see discussion of ultraviolet spectra), and the cation (III ⟷ IV) will possess resonance stabilisation similar to that shown by the



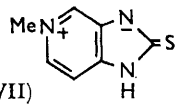
4-aminopyridine cation (V ⟷ VI).[13,14] This resonance stabilisation is also shown by all *N*-methyl derivatives (in the 3-methyl derivative it will be a vinylogous type), and the parent and *N*-methyl derivatives have similar pK_a values. 6-Chloro-1,3,5-triazaindene and its *N*-1 and *N*-3 methyl derivatives (which appear from spectroscopic evidence to be protonated in the imidazole ring) give cations which are not stabilised by a 4-aminopyridine-type resonance. If, however, the "third isomer" is the 5-methyl compound, then it must be protonated in the imidazole ring, and some base-strengthening would be expected. Alternatively, the increased basic strength of the "third isomer" could be accounted for by covalent hydration,[5] but no evidence could be found. Thus, rapid adjustment of a solution of the cation (in which hydration is normally preferred [15]) at pH 3·0, to give the neutral molecule at pH 8·8, showed no variation of the spectrum with time.

The relative basic strengths of the nitrogen atoms in 6-chloro- and 2-methylthio-1,3,5-triazaindene were calculated by a recently developed method.[16] The calculated values for N-1, N-3, and N-5 in the 6-chloro-compound are 3·6, 2·7, and −1·0, and in 2-methylthio-1,3,5-triazaindene the values are 3·2, 2·3, and 3·1, respectively. From this it can be concluded that protonation is unlikely to occur on N-5 of 6-chloro-1,3,5-triazaindene, but in 2-methylthio-1,3,5-triazaindene protonation is more likely to involve N-1 or N-5.

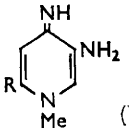
Replacement of hydrogen on nitrogen by methyl in

[13] A. Albert and R. J. Goldacre, *J. Chem. Soc.*, 1946, 706.
[14] A. Albert, R. Goldacre, and J. N. Phillips, *J. Chem. Soc.*, 1948, 2240.
[15] See ref. 5.
[16] D. D. Perrin, *J. Chem. Soc.*, 1965, 5590.

2-mercapto-1,3,5-triazaindene is seen to have little effect on the acid strength of the 1- and 3-methyl compounds, but the 5-methyl compound is a weaker acid by 2·2 pH units. This is attributed to a tendency in the neutral molecule for the aromaticity of the pyridine ring to be preserved, leading to contributions by the dipolar form (VII) and consequent reduction of acidity.



(VII)



(VIII)

The two *N*-methylpyridine compounds (Nos. 22 and 23) have neutral molecules (VIII) which are very strong bases, and their high pK_a values [17] (>14) confirm their structures as the nuclear *N*-1 methyl derivative of the diaminopyridine. Proton addition takes place at the imino nitrogen and is apparently little affected by the 2-chloro-group. (Contrast with the strong base-weakening of 4·35 pH units by a 2-chloro group in 4,5-diaminopyridine [10] and attributed, as in the α-halogenopyridines,[18] to the inductive effect of the chlorine close to the basic centre.) The basic pK_a values governing formation of the di-cation are of the order found for the unmethylated compounds.

EXPERIMENTAL

Analyses were by Dr. J. E. Fildes and her staff. Solids for analysis were dried at 100° unless otherwise stated. M. p.s were taken in Pyrex capillaries. All compounds were examined for the presence of isomers and other impurities by paper chromatography on Whatman Nos. 1 or 4 paper with (a) 3% aqueous ammonium chloride, and (b) butan-2-ol–5N-acetic acid (7 : 3) as solvent.

Ionisation constants were determined (Mr. D. Light) by methods already described.[19] Ultraviolet spectra were measured first on a Perkin-Elmer Spectracord model 4000 recording spectrophotometer, and then $\lambda_{max.}$ and ε values were checked on an Optica CF4 manual instrument (Mr. C. Arandjelovic).

2,4-Dichloropyridine-5-carboxyamide.— 2,4-Dihydroxypyridine-5-carboxylic acid monohydrate [5,20] was converted into the acid chloride,[5] b. p. 120—122°/15 mm., and then into the amide.[5]

5-Amino-2,4-dichloropyridine.—The published method of preparation [5] has been greatly improved. Bromine (19·2 g., 6·2 ml.) was added to potassium hydroxide (14 g.) in water (40 ml.) below −5°, and potassium hydroxide (16·0 g.) in water (56 ml.) added. This solution was dropped into a stirred mixture of 2,4-dichloropyridine-5-carboxyamide (19·1 g.) and water (70 g.) below −5°, and warmed during 2 hr. to 85°, and maintained at 85° for 1·5 hr. Extraction with chloroform gave 5-amino-2,4-dichloropyridine (13·75 g., 84%).

4,5-Diamino-2-chloropyridine.—Reduction of 5-amino-2-chloro-4-hydrazinopyridine [5] with zinc dust (which had been freshly washed with acid) and dilute sulphuric gave reproducible yields of 4,5-diamino-2-chloropyridine.

4,5-Diamino-2-chloro-1-methylpyridinium Iodide.—4,5-Diamino-2-chloropyridine (0·3 g.) was dissolved in methanol (7 ml.), methyl iodide (0·5 ml.) added, and the mixture refluxed for 5 hr. The volatile material was evaporated and the crystalline residue recrystallised from isopropyl alcohol containing a little methanol, to give the *product* (0·35 g.), m. p. 212—213° (Found: C, 25·1; H, 2·8; N, 14·7. $C_6H_9ClIN_3$ requires C, 25·2; H, 3·2; N, 14·7%).

2-Hydroxy-1,3,5-triazaindene.— 3,4-Diaminopyridine [5] (0·5 g.) and urea (1·5 g.) were heated at 165° for 1 hr. The solid residue was recrystallised from water, to give the *product* (0·43 g.), m. p. 304—305° (Found: C, 53·2; H, 4·0; N, 30·9. $C_6H_5N_3O$ requires C, 53·3; H, 3·7; N, 31·1%).

2-Mercapto-1,3,5-triazaindene.—3,4-Diaminopyridine (2 g.), carbon disulphide (15 ml.), and pyridine (50 ml.) were refluxed on a steam-bath for 5 hr. The mixture was evaporated to dryness *in vacuo* and the product purified by dissolution in alkali and reprecipitation at pH 5, to give 2-mercapto-1,3,5-triazaindene (2·68 g.), m. p. >300° (lit.,[6] 370°).

2-Methylthio-1,3,5-triazaindene.—2-Mercapto-1,3,5-triazaindene (0·4 g.) in 2N-sodium hydroxide (5 ml.) was shaken with methyl iodide (0·16 ml., 0·379 g., 1 equiv.) at room temperature for 9 hr. The mixture was cooled, adjusted to pH 7·4, and the white solid recrystallised from water and benzene, to give the *product* (0·275 g., 63%), m. p. 191·5—193·5° (Found: C, 50·6; H, 4·4; N, 25·35; S, 19·3. $C_7H_7N_3S$ requires C, 50·9; H, 4·3; N, 25·4; S, 19·4%). The *picrate*, prepared in ethanol, had m. p. 182—183° (from ethanol) (Found: C, 40·0; H, 2·85; N, 20·9. $C_{13}H_{10}N_6O_7S$ requires C, 39·6; H, 2·6; N, 21·3%).

2-Mercapto-1-methyl-1,3,5-triazaindene.— 3-Amino-4-methylaminopyridine [6] (0·5 g.), carbon disulphide (5 ml.), and pyridine (10 ml.) were refluxed for 1·5 hr., carbon disulphide evaporated, and the pyridine solution heated at 140° for 2 hr. The mixture was then evaporated to dryness and the *product* recrystallised from water (500 ml.), to give 0·63 g., m. p. 346—348° (Found: C, 50·9; H, 4·4; N, 25·3; S, 19·3. $C_7H_7N_3S$ requires C, 50·9; H, 4·3; N, 25·4; S, 19·4%).

1-Methyl-2-methylthio-1,3,5-triazaindene.— 2-Mercapto-1-methyl-1,3,5-triazaindene (0·2 g.) in N-sodium hydroxide (5 ml.) was shaken with methyl iodide (0·15 ml.) for 1 hr. The *product* was extracted with chloroform and recrystallised from light petroleum (b. p. 60—80°), to give 0·083 g., m. p. 98—98·5° (Found: C, 53·9; H, 4·85; N, 23·5; S, 17·8. $C_8H_9N_3S$ requires C, 53·6; H, 5·1; N, 23·4; S, 17·9%). The *picrate*, prepared in ethanol, had m. p. 203—203·5° (from ethanol) (Found: C, 41·0; H, 2·7; N, 20·4. $C_{14}H_{12}N_6O_7$ requires C, 41·2; H, 3·0; N, 20·6%).

2-Mercapto-3-methyl-1,3,5-triazaindene.— 4-Amino-3-methylaminopyridine [6] (0·5 g.), carbon disulphide (5 ml.), and pyridine (10 ml.) were refluxed for 2 hr. The carbon disulphide was evaporated and the pyridine solution heated at 140° for 2 hr. [In the absence of heating at 140°, ring-closure did not take place and the dithiocarbamate was obtained because methylation gave the *methyl dithiocarbamate*, m. p. 215—216° (from benzene) (Found: C, 44·7; H, 5·2; N, 20·1; S, 29·7. $C_8H_{11}N_2S_2$ requires C, 45·05; H, 5·2; N, 19·7; S, 30·1%.] The solvent was evaporated *in vacuo* and the *product* recrystallised from boiling water (175 ml.), to give white crystals (0·635 g.),

[17] S. J. Angyal and C. L. Angyal, *J. Chem. Soc.*, 1952, 1461.
[18] D. H. McDaniel and H. C. Brown, *J. Amer. Chem. Soc.*, 1955, **77**, 3756.
[19] A. Albert and E. P. Serjeant, "Ionization Constants," Methuen, London, 1962.
[20] H. J. den Hertog, J. C. M. Schogt, J. de Bruyn, and A. de Klerk, *Rec. Trav. chim.*, 1950, **69**, 673.

m. p. 315—317° (Found: C, 50·7; H, 4·5; N, 25·9; S, 19·4. $C_7H_7N_3S$ requires C, 50·9; H, 4·3; N, 25·4; S, 19·4%).

3-*Methyl*-2-*methylthio*-1,3,5-*triazaindene*.—To 2-mercapto-3-methyl-1,3,5-triazaindene (0·2 g.) in N-sodium hydroxide (5 ml.), methyl iodide (0·15 ml.) was added and the mixture shaken. The white solid (0·255 g.) was filtered off, washed with water, and recrystallised from light petroleum (b. p. 60—80°), to give the *product*, m. p. 124—125° (Found: C, 53·9; H, 5·0; N, 23·6; S, 18·1. $C_8H_9N_3S$ requires C, 53·6; H, 5·1; N, 23·4; S, 17·9%). The *picrate*, prepared in ethanol, had m. p. 249—251° (from ethanol) (Found: C, 41·0; H, 2·8; N, 21·05; S, 7·5. $C_{14}H_{12}N_6O_7$ requires C, 41·2; H, 3·0; N, 20·6; S, 7·85%).

3,4-*Diamino*-1-*methylpyridinium Iodide*.— 3,4-Diaminopyridine (2 g.) was dissolved in methanol (40 ml.), and the solution cooled, methyl iodide (1·5 ml.) added, and the mixture refluxed for 6 hr. The volatile material was evaporated and the residue recrystallised from isopropyl alcohol containing a little methanol, to give the *product* (3·85 g.), m. p. 194—195° (Found: C, 28·7; H, 3·6; N, 16·55. $C_6H_{10}IN_3$ requires C, 28·7; H, 4·0; N, 16·7%).

2-*Mercapto*-5-*methyl*-1,3,5-*triazaindene*.—To 3,4-diamino-1-methylpyridinium iodide (2 g.) dissolved in pyridine (40 ml.), carbon disulphide (30 ml.) was added and the mixture refluxed for 6 hr. The carbon disulphide was evaporated on a steam-bath and the pyridine solution heated in an oil-bath at 120° for 14 hr. The pyridine was distilled under reduced pressure, the residue dissolved in dilute sodium hydroxide, and addition of hydrochloric acid to pH 10·5 gave the *product* (1·06 g.), m. p. 268—270° (Found, for material dried at 150°/20 mm./2 hr.: C, 50·75; H, 4·4; N, 25·15. $C_7H_7N_3S$ requires C, 50·9; H, 4·3; N, 25·4%). The *hydriodide*, prepared in, and recrystallised from, a small volume of water, had m. p. 263—264° (Found: C, 28·9; H, 2·7. $C_7H_{18}IN_3S$ requires C, 28·7; H, 2·75%).

5-*Methyl*-2-*methylthio*-1,3,5-*triazaindene*.— 2-Mercapto-5-methyl-1,3,5-triazaindene (prepared as described above from 0·5 g. of 3,4-diamino-1-methylpyridinium iodide) was dissolved in N-sodium hydroxide (10 ml.) and shaken with methyl iodide (1·2 ml.) for 1·5 hr. The solution was extracted with chloroform, and the *product* obtained crystallised from benzene to give 0·165 g. (Found: C, 53·3; H, 5·0; N, 23·4. $C_8H_9N_3S$ requires C, 53·6; H, 5·1; N, 23·4%). The *hydriodide*, prepared in ethanol, had m. p. 219—221° (from ethanol) (Found: C, 31·4; H, 3·4; N, 13·75; S, 10·4. $C_8H_{10}IN_3S$ requires C, 31·3; H, 3·3; N, 13·7; S, 10·4%). The *picrate*, prepared in ethanol, had m. p. 211—212·5° (from ethanol) (Found: C, 41·3; H, 3·0; N, 20·3; S, 7·6. $C_{14}H_{12}N_6O_7S$ requires C, 41·2; H, 3·0; N, 20·6; S, 7·85%).

2-*Mercapto*-1,3,5-*triazaindene with Excess Diazomethane*.—Diazomethane in cold ether (prepared from 5 g. of nitrosomethylurea) was added to 2-mercapto-1,3,5-triazaindene (1·0 g.) in methanol (100 ml.) cooled in ice, and after 2 hr. at 1° it was evaporated to dryness. The product was chromatographed in chloroform on alumina (15 in.).

The main product was eluted last, and after recrystallisation from benzene gave 5-methyl-2-methylthio-1,3,5-triazaindene (0·51 g.), m. p. and mixed m. p. 165·6—167° (Found: C, 53·65; H, 5·0; N, 23·3; S, 17·6. Calc. for $C_8H_9N_3S$: C, 53·6; H, 5·1; N, 23·4; S, 17·9%).

The earlier fractions (0·42 g.) were further purified by chromatography and gave first, on recrystallisation from light petroleum (b. p. 60—80°), 3-methyl-2-methylthio-1,3,5-triazaindene, m. p. and mixed m. p. 124—125°, and later fractions gave, with ethanolic picric acid, 1-methyl-2-methylthio-1,3,5-triazaindene picrate, m. p. and mixed m. p. 204—205°. Similar results were obtained when methyl iodide in alkali was used as methylating agent.

4-*Chloro*-1,3,5-*triazaindene*.— 3,4-Diamino-2-chloropyridine [21] (0·2 g.), triethyl orthoformate (1·4 ml.), and acetic anhydride (1·4 ml.) were refluxed for 3 hr. Excess reagents were then removed *in vacuo* and the crystalline residue warmed with 2·5N-sodium hydroxide (5 ml.) at 40—50° for 10 min., cooled, adjusted to pH 5, and chilled overnight. The crystalline solid (0·1623 g.) was recrystallised from a small quantity of boiling water, to give the *product*, m. p. 217—218° (decomp.) (Found: C, 47·25; H, 2·6; Cl, 23·3; N, 27·4. $C_6H_4ClN_3$ requires C, 46·9; H, 2·6; Cl, 23·1; N, 27·35%). The picrate, prepared in ethanol, had m. p. 179° (from ethanol) (lit.,[22] 179—181°).

6-*Chloro*-1,3,5-*triazaindene*.— 4,5-Diamino-2-chloropyridine (0·2 g.) was added to triethyl orthoformate (1·4 ml.) and acetic anhydride (1·4 ml.), and refluxed for 3 hr. Excess reagent was distilled under reduced pressure, and the crystalline residue dissolved in 2·5N-sodium hydroxide and warmed at 40—50° for 10 min. After chilling, the mixture was adjusted to pH 5 and the precipitate collected and recrystallised from water, to give pale yellow crystals of the *product* (0·19 g.), m. p. 236—238° (Found: C, 47·0; H, 2·5; Cl, 23·0; N, 27·1. $C_6H_4ClN_3$ requires C, 46·9; H, 2·6; Cl, 23·1; N, 27·35%).

The chlorine atom in 6-chloro-1,3,5-triazaindene is unreactive and is unchanged on refluxing with 2N-sodium hydroxide or hydrazine hydrate, or on heating with 5N-hydrochloric acid at 210°.

6-*Chloro*-2-*methyl*-1,3,5-*triazaindene*.— 4,5-Diamino-2-chloropyridine (0·2 g.), acetic anhydride (1·4 ml.), and triethyl orthoacetate (1·2 ml.) were refluxed for 3·5 hr. and then evaporated to dryness under reduced pressure. The residue was warmed with 2·5N-sodium hydroxide (5 ml.) at 40—50° for 10 min., cooled, and adjusted to pH 5. After refrigeration overnight, the crystalline solid (0·104 g.) was filtered off and recrystallised from a small volume of boiling water, to give the *product*, m. p. 216—217° (Found: C, 50·1; H, 3·7; Cl, 21·5; N, 25·3. $C_7H_6ClN_3$ requires C, 50·2; H, 3·6; Cl, 21·15; N, 25·1%).

6-*Chloro*-2-*hydroxy*-1,3,5-*triazaindene*.—A mixture of 4,5-diamino-2-chloropyridine (0·1 g.) and urea (0·3 g.) was heated at 165° for 1 hr. The *product* was purified by dissolution in dilute sodium hydroxide and reprecipitated at pH 5, to give 0·067 g., m. p. >350° (Found: C, 42·3; H, 2·2; Cl, 21·1; N, 24·7. $C_6H_4ClN_3O$ requires C, 42·5; H, 2·4; Cl, 20·9; N, 24·8%).

6-*Chloro*-2-*mercapto*-1,3,5-*triazaindene*.— 4,5-Diamino-2-chloropyridine (0·125 g.), carbon disulphide (1·25 ml.), and pyridine (3·75 ml.) were refluxed for 5·5 hr., and the mixture was evaporated to dryness. The *product* was washed thoroughly with water, and purified by reprecipitation (at pH 5) from an alkaline solution, to give 0·12 g., m. p. >320° (Found: C, 38·5; H, 2·2; Cl, 18·85; S, 16·9. $C_6H_4ClN_3S$ requires C, 38·8; H, 2·2; Cl, 19·1; S, 17·3%).

6-*Chloro*-2-*methylthio*-1,3,5-*triazaindene*.—Methyl iodide (0·18 ml.) was shaken with a mixture of 6-chloro-2-mercapto-1,3,5-triazaindene (0·25 g.) in N-sodium hydroxide (2·5 ml.) for 3 hr., and then the solution adjusted to pH 5·0. The precipitate of the *product* (0·22 g.) was further purified

[21] O. Bremer, *Annalen*, 1935, **518**, 274.
[22] C. A. Salemink and G. M. van der Want, *Rec. Trav. chim.*, 1949, **68**, 1013.

by reprecipitation, m. p. 238·5—240° (Found: C, 42·15; H, 2·9; Cl, 18·0; S, 16·3. $C_7H_6ClN_3S$ requires C, 42·1; H, 3·0; Cl, 17·75; S, 16·0%).

2,6-*Dichloro*-1,3,5-*triazaindene*.—Chlorine was passed through a slurry of 6-chloro-2-methylthio-1,3,5-triazaindene (0·2 g.), methanol (0·5 ml.), and 10N-hydrochloric acid (1·5 ml.) maintained below −10°. The solid dissolved in 15 min. and the chlorine was passed for 35 min. The solution was poured on to ice (4 g.) and below −10° ammonium hydroxide was added to pH 5·4, and the solution refrigerated overnight. The yellow solid (0·18 g.) was collected and purified by precipitation at pH 5·4 from alkaline solution to give the *product*, m. p. 234—235° (decomp.) (Found: C, 38·75; H, 1·5; N, 22·3. $C_6H_3Cl_2N_3$ requires C, 38·3; H, 1·6; N, 22·35%).

Methylation of 6-*Chloro*-1,3,5-*triazaindene*.—Diazomethane in ether (prepared from 3 g. of nitrosomethylurea) was added to a cold solution of 6-chloro-1,3,5-triazaindene (1 g.) dissolved in methanol (30 ml.), and the mixture allowed to stand 2 hr. at 1°. The solvent was evaporated and the products chromatographed in chloroform on alumina (15 in.). The first fractions gave, in the following order, on recrystallisation from benzene–light petroleum (b. p. 60—80°), 6-*chloro*-3-*methyl*-1,3,5-*triazaindene* (0·25 g.), m. p. 166·5—168° (Found: C, 50·1; H, 3·8; Cl, 21·4; N, 25·15. $C_7H_6ClN_3$ requires C, 50·2; H, 3·6; Cl, 21·15; N, 25·1%), and 6-*chloro*-1-*methyl*-1,3,5-*triazaindene* (0·17 g.), m. p. 188·5—190° (Found: C, 50·05; H, 3·8; Cl, 21·2; N, 25·3%). [Mixtures of the 1- and 3-methyl isomers only are best separated by chromatography in benzene on alumina (5 in.), and the 3-methyl isomer is eluted first. The R_F values of the 3- and 1-methyl isomers are indistinguishable on paper chromatography in butanol–acetic acid and aqueous ammonium chloride, but the 3-methyl isomer exhibits a bright fluorescence under the 365 mμ lamp and the 1-methyl isomer does not.] Later fractions from the chloroform chromatogram gave 6-*chloro*-?-*methyl*-1,3,5-*triazaindene* (0·16 g.) which crystallised from benzene as white needles, and after drying at 100° had m. p. 170—171° (decomp.) (Found: C, 49·95; H, 3·6; Cl, 21·0; N, 25·1%).

1-*Methyl*-1,3,5-*triazaindene*.— (*a*) 3-Amino-4-methylaminopyridine was refluxed with formic acid as described by Mizuno *et al.*[7], and the white product obtained by sublimation was chromatographed in chloroform on alumina (6 in.) and recrystallised from benzene, to give 1-methyl-1,3,5-triazaindene, m. p. 115—116° (lit.,[7] 111·5—112·5°). The picrate, prepared in ethanol, had m. p. 219—220·5° (from ethanol) (lit.,[7] 217—218°).

(*b*) 6-Chloro-1-methyl-1,3,5-triazaindene (0·056 g.), anhydrous sodium acetate (0·2 g.) and 10% palladium–charcoal (0·2 g.) were shaken in methanol (10 ml.) with hydrogen at room temperature and pressure for 36 hr. The catalyst was filtered off and washed with boiling methanol, and the filtrate evaporated to dryness. The product was extracted with benzene and recrystallised from benzene–light petroleum (b. p. 60—80°), to give needles of 1-methyl-1,3,5-triazaindene (0·022 g.), m. p. 115—116°. Picrate, m. p. 216·5°, was identical with that prepared above.

3-*Methyl*-1,3,5-*triazaindene*.— (*a*) 4-Amino-3-methylaminopyridine (0·5 g.) and formic acid (1 ml.; 98—100%) were refluxed for 1 hr. Excess formic acid was distilled and the product sublimed at 160°/0·5 mm. The sticky product was dissolved in ethanol and the addition of ethanolic picric acid gave 3-methyl-1,3,5-triazaindene picrate (1·28 g.), m. p. 204·5—205·5° (from ethanol) (lit.,[7] 199·5—200°). The picrate was dissolved in dilute sodium hydroxide, and extraction with chloroform gave, after recrystallisation from light petroleum (b. p. 60—80°), 3-methyl-1,3,5-triazaindene, m. p. 101—102·5° (lit.,[7] 101—101·5°).

(*b*) 6-Chloro-3-methyl-1,3,5-triazaindene (0·059 g.), anhydrous sodium acetate (0·2 g.), 10% palladium–charcoal (0·2 g.), and methanol (10 ml.) were shaken with hydrogen at room temperature and pressure for 36 hr. The catalyst was filtered off and washed with boiling methanol, and the combined filtrates were evaporated to dryness. The product was extracted in benzene and recrystallised from light petroleum (b. p. 60—80°), to give 3-methyl-1,3,5-triazaindene (0·026 g.), m. p. 100—101°. Picrate, prepared in ethanol, had m. p. 202—203·5° (from ethanol) not depressed on admixture with the picrate prepared above.

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