Acknowledgments.—The authors express their appreciation to Dr. W. C. Coburn, Jr., for helpful discussions, to Dr. J. A. Montgomery for encouragement in this work, to Mr. W. E. Fitzgibbon and associates of the Organic Preparations Section for preparing large quantities of intermediates, to Miss Kathleen Hewson and associates for paper chromatography, and to Drs. W. J. Barrett, W. C. Coburn, Jr., and P. D. Sternglanz of the Analytical Section of this Institute for elemental analyses and absorption spectra.

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

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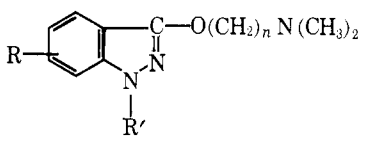
Thirty-four 1-substituted 3-dimethylaminoalkoxy-1H-indazoles have been synthesized and pharmacologically evaluated. Some of them proved to be interesting analgesic, antiinflammatory, and antispasmodic agents of low toxicity.

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



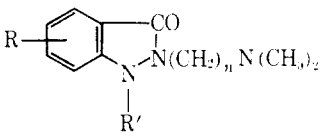
I

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).

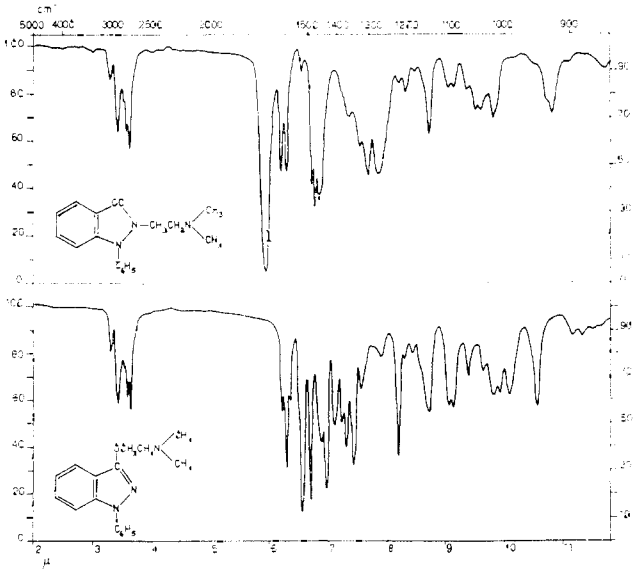


Figure 1.—Infrared spectra of 2-β-dimethylaminoethyl-1-phenylindazolin-3-one and of 3-β-dimethylaminoethoxy-1-phenyl-1H-indazole determined in CCl_4.

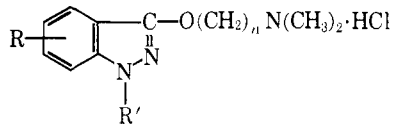
(1) L. Baiocchi, G. Corsi, and G. Palazzo, *Ann. Chim.* (Rome), **55**, 116 (1965).

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

Pharmacology.—The products described in this paper and listed in Table I have been submitted to a preliminary pharmacological screening. The following methods were used.

TABLE I

3-DIALKYLAMINOALKOXY-1H-INDAZOLE HYDROCHLORIDES



No.	R	R′	n	M.p., °C.	Formula	Cl⁻, % Calcd.	Cl⁻, % Found
1	H	CH_3	2	161	$C_{12}H_{18}ClN_3O$	13.87	13.73
2	H	CH_3	3	150	$C_{13}H_{20}ClN_3O$	13.14	13.18
3	H	C_4H_9	3	109	$C_{16}H_{26}ClN_3O$	11.37	11.42
4	H	C_6H_5	2	175	$C_{17}H_{20}ClN_3O$	11.16	10.98
5	H	C_6H_5	3	197	$C_{18}H_{22}ClN_3O$	10.69	10.60
6	H	$C_6H_5CH_2$	2	155	$C_{18}H_{22}ClN_3O$	10.69	10.81
7	H	$C_6H_5CH_2$	3	159	$C_{19}H_{24}ClN_3O$	10.25	10.29
8	H	o-$ClC_6H_4CH_2$	3	157	$C_{19}H_{23}Cl_2N_3O$	9.32	9.24
9	H	m-$ClC_6H_4CH_2$	3	97	$C_{19}H_{23}Cl_2N_3O$	9.32	9.21
10	H	p-$ClC_6H_4CH_2$	2	155	$C_{18}H_{21}Cl_2N_3O$	9.68	9.66
11	H	p-$ClC_6H_4CH_2$	3	120	$C_{19}H_{23}Cl_2N_3O$	9.32	9.52
12	H	p-$CH_3OC_6H_4CH_2$	2	215	$C_{19}H_{24}ClN_3O_2$	9.80	9.76
13	H	p-$CH_3OC_6H_4CH_2$	3	120	$C_{20}H_{26}ClN_3O_2$	9.43	9.40
14	H	3,4-$(CH_3O)_2C_6H_3CH_2$	3	111	$C_{21}H_{28}ClN_3O_3$	8.73	8.59
15	H	$C_6H_5CH_2CH_2$	2	181	$C_{19}H_{24}ClN_3O$	10.25	10.29
16	H	$C_6H_5CH_2CH_2$	3	163	$C_{20}H_{26}ClN_3O$	9.85	9.91
17	4-Cl	$C_6H_5CH_2$	3	160	$C_{19}H_{23}Cl_2N_3O$	9.32	9.37
18	5-Cl	C_4H_9	2	122	$C_{15}H_{23}Cl_2N_3O$	10.67	10.43
19	5-Cl	C_4H_9	3	139	$C_{16}H_{25}Cl_2N_3O$	10.24	10.39
20	5-Cl	$C_6H_5CH_2$	2	195	$C_{18}H_{21}Cl_2N_3O$	9.68	9.80
21	5-Cl	$C_6H_5CH_2$	3	160	$C_{19}H_{23}Cl_2N_3O$	9.32	9.50
22	5-Cl	p-$CH_3OC_6H_4CH_2$	2	130	$C_{19}H_{23}Cl_2N_3O_2$	8.96	9.12
23	5-Cl	p-$CH_3OC_6H_4CH_2$	3	117	$C_{20}H_{25}Cl_2N_3O_2$	8.64	8.54
24	6-Cl	C_4H_9	2	133	$C_{15}H_{23}Cl_2N_3O$	10.67	10.47
25	6-Cl	$C_6H_5CH_2$	2	199	$C_{18}H_{21}Cl_2N_3O$	9.68	9.68
26	6-Cl	$C_6H_5CH_2$	3	141	$C_{19}H_{23}Cl_2N_3O$	9.32	9.54
27	6-Cl	p-$ClC_6H_4CH_2$	2	190	$C_{18}H_{20}Cl_3N_3O$	8.84	8.84
28	6-Cl	p-$ClC_6H_4CH_2$	3	125[a]			
29	7-Cl	$C_6H_5CH_2$	3	151	$C_{19}H_{23}Cl_2N_3O$	9.32	9.41
30	5-NH_2	C_4H_9	3	223	$C_{16}H_{25}Cl_2N_4O$[b]	19.52	19.33
31	5-NH_2	$C_6H_5CH_2$	3	215	$C_{19}H_{26}Cl_2N_4O$[b]	17.41	17.41
32	5-CH_3O	$C_6H_5CH_2$	3	155	$C_{20}H_{26}ClN_3O_2$	9.43	9.36
33	5-NO_2	C_4H_9	3	200	$C_{16}H_{25}ClN_4O_3$	9.93	10.04
34	5-NO_2	$C_6H_5CH_2$	3	188	$C_{19}H_{23}ClN_4O_3$	9.07	8.95

[a] Citrate. [b] ·2HCl.

Acute toxicity and general effects on behavior were studied in mice that were examined 0.5 hr. after administration and then observed for 5 days for delayed toxic effects. **Anticonvulsive action** was studied in mice, using electroshock convulsions[3] and convulsions and death induced by pentylenetetrazole (120 mg./kg. s.c.) and strychnine (2.5 mg./kg. s.c.). **Antispasmodic action** was investigated in segments of guinea pig small intestine suspended in oxygenated Tyrode solution and stimulated with acetylcholine, histamine, barium chloride, and dimethylphenylpiperazinium iodide. **Analgesic action** was studied using the hot plate[4] and the phenylquinone methods.[5] **Antiinflammatory action** was investigated by the effects on plantar edema induced by carragenin in the rat[6] and on the cotton pellet induced granuloma.[7] **Local anesthetic action** was studied using the corneal reflex in rabbits for surface anesthesia and the tail pinching test in mice for infiltration anesthesia.

The results obtained make it difficult to establish a clear relationship between chemical structure and biological activity. Therefore only a general outline of the different types of activity exhibited by the members of the series will be mentioned.

Toxicity proved to be fairly constant in all series, varying from 120–150 mg./kg. i.p., with the exception of the compounds having a nitro group or an amino group in the indazole nucleus. These derivatives were considerably more toxic and provoked cyanosis. Lethal effects generally were manifest within 1–2 hr. after administrations and were accompanied by a complex symptomatology characterized by the presence of convulsive and depressive phenomena.

As for behavioral effects, the differences between

(3) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exptl. Therap.*, **106**, 319 (1952).

(4) G. Woolfe and A. D. MacDonald, *ibid.*, **80**, 300 (1944).

(5) (a) E. Siegmund, R. Cadmus, and G. Lu, *Proc. Soc. Exptl. Biol. Med.*, **95**, 729 (1957); (b) L. C. Hendershot and J. Forsaith, *J. Pharmacol. Exptl. Therap.*, **125**, 237 (1959).

(6) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exptl. Biol. Med.*, **111**, 544 (1962).

(7) R. Meier, W. Shuler, and P. Desaulles, *Experientia*, **6**, 469 (1950)

the various members of the series were relatively slight. Doses of 20–40 mg./kg. i.p. produced sedation, muscle relaxation, and motor incoordination, whereas doses of 80–100 mg./kg. produced depression. Clonic convulsions were produced at almost lethal doses. Significant effects on the autonomic nervous system were not observed.

The analgesic action represents an interesting characteristic of the products of the series. Whereas all of the compounds are active in the phenylquinone test at high doses (80–100 mg./kg. s.c.), for **2**, **4–7**, **9**, **11–13**, **15**, **16**, **21**, and **26** (Table I), the ED_{50} is within the range 20–40 mg./kg. s.c. (confidence limits not higher than 20%). This means that none of them possesses an activity comparable to that of morphine, which is active at 1 mg./kg. s.c., but that most of them are clearly more active than aspirin, the ED_{50} of which is 61 (50–74) mg./kg. Here again there is no clear relationship between activity and structure, but the more toxic substances mentioned above are less active, and the derivatives with dimethylaminoethoxy side chains are less active than the corresponding dimethylaminopropoxy substances.

Several of the products possess a significant antiinflammatory action. It was not possible, however, to establish a significant correlation between analgesic and antiinflammatory activity. For instance, compounds **10** and **17–19**, which are not among the most active analgesics, display an antiinflammatory activity at the same dose of 15 mg./kg. s.c. as **2**, **4**, **7**, and **26**.

The most active anticonvulsant compounds in electroshock tests and tonic convulsions induced by strychnine are **4**, **7**, **15**, and **19**, which possess an ED_{50} lower than 40 mg./kg. i.p. At these doses none of the compounds protected against death induced by strychnine or convulsions and death induced by pentamethylenetetrazole.

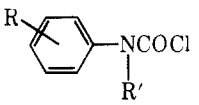
Remarkable variations of activity were found in the tests for antispasmodic and local anesthetic activity. The latter is present in varying degree in the various products of the series. Compounds **5–7**, **10**, **15**, **20**, and **31** are active at concentrations below 0.5 mg./ml. both in the surface and infiltration tests. By contrast, **12**, **24**, and **30** are inactive up to concentrations of 10 mg./ml., and they cause local irritation.

All of the products inhibit intestinal-strip contractions at concentrations of 0.2–0.3 μg./ml., with the exception of **27**, **28**, and **33** which are active at 5 μg./ml. and of **30** which even at this concentration is almost inactive. The effect must be considered as being of the papaverine type, since the contractions induced by acetylcholine, histamine, barium chloride, and dimethylphenylpiperazinium iodide are inhibited at the same concentrations. Under the same experimental conditions, papaverine proves to be active at concentrations of 4–7 μg./ml. The lack of antihistamine activity is somewhat unexpected, because of the similarity of our series with several antihistamine substances, such as the phthalazines described by Lenke.[8] It is interesting that Lenke compared some products having an aminoalkyl chain at the oxygen with isomers having the chain at the nitrogen, and found a greater biological activity in the latter. In our case, although with different pharmacological tests, the opposite occurs. The two substances of formula II are less active than the corresponding derivatives I in terms of analgesic and antiinflammatory properties which are the most striking and characteristic ones of the series.

Experimental Section

Carbamoyl chlorides were prepared by the action of $COCl_2$ on substituted anilines. The preparations were usually carried out in toluene and in the presence of pyridine, as has been previously described for analogous products.[1] The characteristics of the substances not previously described are shown in Table II.

TABLE II
CARBAMOYL CHLORIDES



R	R'	B.p. (mm.) or m.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % Cl	Found, % C	Found, % H	Found, % Cl
H	*o*-$ClC_6H_4CH_2$	60	$C_{14}H_{11}Cl_2NO$	60.02	3.96	25.31	60.04	3.87	
H	*m*-$ClC_6H_4CH_2$	160 (0.4)	$C_{14}H_{11}Cl_2NO$	60.02	3.96	25.31			25.32
H	*p*-$ClC_6H_4CH_2$	70	$C_{14}H_{11}Cl_2NO$	60.02	3.96	25.31			25.41
H	*p*-$CH_3OC_6H_4CH_2$	172 (0.3)	$C_{15}H_{14}ClNO_2$	65.34	5.12		65.69	5.54	
H	3,4-$(CH_3O)_2C_6H_3CH_2$	129	$C_{16}H_{16}ClNO_3$			11.60			11.80
p-Cl	C_4H_9	124 (0.2)	$C_{11}H_{13}Cl_2NO$	53.67	5.32	28.81	54.21	5.43	28.89
p-Cl	*p*-$CH_3OC_6H_4CH_2$	175 (1)	$C_{15}H_{13}Cl_2NO_2$	58.08	4.23		58.30	4.44	
p-NO_2	C_4H_9	146 (0.1)	$C_{11}H_{13}ClN_2O_3$			13.81			13.64

3-Hydroxy-1H-indazoles. A.—The carbamoyl chlorides were transformed to the corresponding azides which were then decomposed in tetralin as already described.[1] In the pyrolysis also the 1-substituted benzimidazolin-2-ones were generally formed and discarded, except in the case of N-(*p*-methoxyphenyl)-N-methylcarbamoyl azide, 5-methoxy-1-methyl-benzimidazolin-2-one, m.p. 204° (from ethanol), was isolated and identified.

Anal. Calcd. for $C_9H_{10}N_2O_2$: C, 60.86; H, 5.66; N, 15.72. Found: C, 60.80; H, 5.71; N, 15.88.

B.—The preparation involved first nitrosation of anthranilic acids and subsequent reduction with sodium hydrosulfite. Two anthranilic acids that have not yet been described were prepared as follows.

4-Chloro-2-(*p*-chlorobenzylamino)benzoic Acid.—To a solution of 0.1 mole of sodium 2-amino-4-chlorobenzoate in 100 ml. of water at 50°, 0.1 mole of *p*-chlorobenzyl chloride was added (stirring) over a period of about 30 min. After the addition, the temperature was raised to 70° where it was kept for 4 hr. The mixture was cooled, and the precipitated solid was collected with suction, washed with water, and crystallized from ethanol; yield 75%, m.p. 198°.

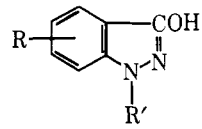
Anal. Calcd. for $C_{14}H_{11}Cl_2NO_2$: C, 56.77; H, 3.74; N, 4.79. Found: C, 56.77; H, 4.10; N, 4.76.

2-Butylamino-4-chlorobenzoic Acid. A.—2-Amino-4-chloro-

(8) H. Lenke, *Arzneimittel-Forsch.*, **7**, 678 (1957).

TABLE III

3-HYDROXY-1H-INDAZOLES



R	R′	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	Method[a]
H	C_4H_9	109	$C_{11}H_{14}N_2O$	69.44	7.42	14.73	69.62	7.35	14.91	B
H	*o*-$ClC_6H_4CH_2$	231	$C_{14}H_{11}ClN_2O$	64.99	4.29	10.83	64.83	4.30	11.05	A
H	*m*-$ClC_6H_4CH_2$	151	$C_{14}H_{11}ClN_2O$	64.99	4.29	10.83	65.22	4.63	10.93	A
H	*p*-$ClC_6H_4CH_2$	178	$C_{14}H_{11}ClN_2O$	64.99	4.29	10.83	65.03	4.41	10.83	A
H	*p*-$CH_3OC_6H_4CH_2$	161	$C_{15}H_{14}N_2O_2$	70.85	5.55	11.02	71.08	5.82	11.29	A
H	3,4-$(CH_3O)_2C_6H_3CH_2$	163	$C_{16}H_{16}N_2O_3$	67.59	5.67	9.85	67.29	5.35	10.06	A
5-Cl	C_4H_9	120	$C_{11}H_{13}ClN_2O$	58.80	5.83	12.47	58.85	5.97	12.54	A
5-Cl	*p*-$CH_3OC_6H_4CH_2$	199	$C_{15}H_{13}ClN_2O_2$	62.40	4.54	9.70	62.67	4.87	10.03	A
6-Cl	C_4H_9	171	$C_{11}H_{13}ClN_2O$	58.80	5.83	12.47	58.65	5.77	12.64	B
6-Cl	*p*-$ClC_6H_4CH_2$	236	$C_{14}H_{10}Cl_2N_2O$	57.36	3.44	24.19	57.10	3.67	23.94	B
5-NO_2	C_4H_9	252	$C_{11}H_{13}N_3O_3$	56.16	5.57	17.86	56.36	5.85	17.40	A

[a] See Experimental Section.

benzoic acid (0.1 equiv.), 0.1 equiv. of K_2CO_3, 0.11 equiv. of butyl bromide, and 330 ml. of water were refluxed with stirring for 20 hr. The mixture was cooled and the separated product was filtered, washed with water, and crystallized from ethanol; yield 50%, m.p. 135°.

Anal. Calcd. for $C_{11}H_{14}Cl_2NO_2$: Cl, 15.57; N, 6.15. Found: Cl, 15.54; N, 6.06.

B.—To 125 ml of an aqueous solution of 0.1 mole of sodium N-substituted anthranilate, 0.15 mole of $NaNO_2$ was added with stirring to complete solution. To the solution maintained at 10–15°, 36 ml. of concentrated HCl was added slowly over a period of at least 30 min. Stirring was continued for another 0.5 hr. The precipitate was then filtered, and the nitrous derivative was washed with cold water and used for the subsequent operation without further purification. With vigorous stirring, it was added to 400 ml. of a 20% solution of NaOH at 70°. Immediately 0.5 mole of crystalline sodium hydrosulfite was added all at once. Heating was continued for 2 hr. The reaction mixture was cooled and the precipitate was filtered. It was treated with water and the mixture was made clearly acid with concentrated HCl. The crystalline product was filtered, washed, and crystallized from ethanol; yield 70–80%. The characteristics of the 3-hydroxy-1H-indazoles that have not yet been described are shown in Table III.

3-Dimethylaminoalkoxy-1H-indazoles.—The sodium salt of a 1-substituted 3-hydroxy-1H-indazole was prepared with the calculated quantity of sodium methoxide in methanol, eliminating the solvent under reduced pressure. The solid sodium salt (0.1 mole) was dried in an oven, well powdered, and suspended in 1 vol. of anhydrous xylene equal to 10 times its weight. Under fairly vigorous stirring and refluxing, 0.13 mole of chloroalkyldimethylamine diluted with 2 vol. of solvent was added from a dropping funnel (average time for this operation 1.5 hr.), after which heating and stirring were continued for 2 hr. The mixture was cooled and washed well with water, and the basic fraction was extracted with 2 *N* HCl. The base, liberated from the HCl solution by addition of 2 *N* NaOH, was extracted with ether, washed, and dried. The residue was distilled and the distillate, dissolved in 10 vol. of $CHCl_3$, was passed over an alumina column (Merck, standardized according to Brockmann). More $CHCl_3$ was used for elution and the solvent was evaporated. The residue was usually a product completely free of the infrared carbonyl band. In a few cases a second or even a third passage over Al_2O_3 was required to obtain compound I completely free of isomer II. It was transformed to the hydrochloride, which was then crystallized from ethanol. An example for the isolation of the by-products is reported below.

2-β-Dimethylaminoethyl-1-phenylindazolin-3-one.—The basic residue of a preparation carried out following the general method previously described, using 150 g. of 3-hydroxy-1-phenyl-1H-indazole and 90 g. of chloroethyldimethylamine, was dissolved in anhydrous ethanol and treated with a 30% alcoholic H_3PO_4 corresponding to the weight of the residue. The precipitate was filtered and crystallized from alcohol. After a second crystallization from water, 140 g. of a product, m.p. 130–133°, was obtained. The product had analytical values corresponding to 3-β-dimethylaminoethoxy-1-phenyl-1H-indazole phosphate monohydrate. The infrared spectrum was without carbonyl bands. The remaining alcoholic solutions from the preparation and from the crystallization of the phosphate were combined, and the solvent was removed. The residue was dissolved in water and the base was liberated with K_2CO_3. Distillation yielded a product boiling at 192° (0.1 mm.) which solidified in the flask. It crystallized from hexane–benzene; yield 35 g., m.p. 90°, carbonyl band (KBr) at 1690 $cm.^{-1}$.

Anal. Calcd. for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.97. Found: C, 72.76; H, 7.00; N, 14.68.

The **hydrochloride**, crystallized from isopropyl alcohol, melted at 217–219°.

Anal. Calcd. for $C_{17}H_{20}ClN_3O$: Cl (ionic), 11.15. Found: Cl (ionic), 11.13.