We have also studied the absorption spectra in the ultraviolet, of the above solutions at 15 and 51°, and in some cases at 25°. The spectra show peaks at 240 ± 0.5 mμ and 335 ± 0.5 mμ. We have established that the peak at 335 mμ is almost entirely due to the dimer, and that the one at 240 mμ is due to contributions both from Fe^{3+} and $FeOH^{2+}$. The results have been used to evaluate $K_{2,2}$ at 15 and 51°, and these are found to be in agreement with those obtained from the magnetic data. The value obtained at 25° from magnetic data is in reasonable agreement with that reported by Hedström.

This work adds to the small group of known substances or ions in which exchange effects destroy all the paramagnetism normally present in iron (III). It also suggests that the well known subnormal magnetic moment for the iron in hydrous ferric oxide[4] may be due to part of the iron being present as dimers built into the gel structure. Just prior to precipitation almost half the iron in a 0.04 *M* solution is present as dimer.

This work was performed under contract with the Signal Corps Engineering Laboratories, Army Signal Corps.

(4) P. W. Selwood, M. Ellis and K. Wethington, THIS JOURNAL, **71**, 2181 (1949).

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RECEIVED NOVEMBER 6, 1954

FUROCHROMONES AND COUMARINS. XI. THE MOLLUSCICIDAL ACTIVITY OF BERGAPTEN, ISOPIMPINILLIN AND XANTHOTOXIN

Sir:

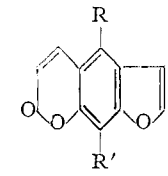
Though several thousands of synthetic organic compounds have been screened for molluscicidal activity, very little is known about the activity of naturally occurring compounds. We have investigated the molluscicidal activity of the naturally occuring furocoumarins, *e.g.*, bergapten (I), isopimpinillin (II) and xanthotoxin (III) against *Biomphalaria boissi*, the intermediate host of *Schistosoma mansoni* (Bilharzia) in Egypt. It was found that the molluscicidal power of bergapten and isopimpinillin is of the same order of magnitude as that of the most powerful synthetic organic compounds, *e.g.*, dinitro-*o*-cyclohexylphenol and sodium pentachlorophenate, I being stronger than II, III being less potent. I, II and III are neither caustic nor irritating as is the case with many synthetic molluscicides.

These findings may explain—at least in part—the role of furocoumarins in the vegetable kingdom (protection of plants against snails) and may open a new method in the control of *Biomphalaria boissi*, namely, by growing plants which contain these active furocoumarins and after harvesting throwing the plants into the channels infected by the snails (*Biomphalaria boissi*).

Egyptian plants are known to contain active furocoumarins, *e.g.*, *Ammi majus* L contains xanthotoxin.[1]

(1) A. Schönberg and A. Sina, *Nature*, **161**, 481 (1948).

I, R = OCH_3, R′ = H
II, R = R′ = OCH_3
III, R′ = OCH_3, R = H



The results of our preliminary experiments were confirmed and extended by Dr. G. T. Evans and Mr. R. Zachary from the United States Naval Medical Research Unit No. 3 (Cairo) to whom we are greatly indebted. Their results are given below:

Test Conditions.—Compare D. O. Hoffman and R. Zachary, *Am. J. Trop. Med. and Hyg.*, **2**, 332 (1953). Test temperature 26°. Exposure period 24 hours in the presence of the chemical followed by 72 hours observation period in fresh pond water.

Chemical solutions were made in acetone, an aliquot taken and diluted to the desired concentration. The solvent in itself was not toxic to snails at the dose used.

Snails used were obtained from a drain (natural habitat) near the village of Geziret Mohammed and stocked in out-door concrete ponds fitted for snail colonization. Natural water was used after being filtered through a cotton layer. The percentage figures refer to snails killed.

TABLE I

Compound	p.p.m. = parts per million 5 p.p.m.	2 p.p.m.
I	32/32 (100%)	22/32 (69%)
II	22/32 (69%)	3/32 (9%)
DCHP[2]	13/16 (81%)	14/32 (44%)
DOW G[3]	10/16 (63%)	2/32 (6%)

III in a concentration of 10 p.p.m. and under the above conditions killed only 25% (4/16) of the snails tested and 0% (0/16) in a concentration of 5 p.p.m. The kill was 100% (10/10) when the concentration was 50 p.p.m. and the exposure and observation periods were 24 hours.

(2) DCHP = Dinitro-*o*-cyclohexylphenol, R. E. Kuntz, *The Lebanese Medical Journal*, 46 (1952); R. E. Kuntz and M. A. Stirewalt, *Proc. Helminth. Soc. Washington*, **17**, 95 (1950).

(3) Dow G. = Sodium pentachlorophenate, A. Halawani, N. Latif and T. Anwar, *J. Roy. Egypt. Med. Assoc.*, **34**, 163 (1951); E. G. Berry, M. O. Nolan and O. Gonzales, *Health Repts.*, **65**, 939 (1950).

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RECEIVED JUNE 28, 1954

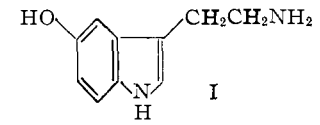
THE ACTION OF OXALYL CHLORIDE ON INDOLES: A NEW APPROACH TO TRYPTAMINES

Sir:

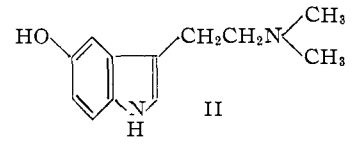
Interest in the physiological actions of tryptamine derivatives has been stimulated considerably by the proposals of Woolley and Shaw[1] and Gaddum[2] that serotonin (I) may play a role in central nervous system function. The possibility that the remarkable hallucinogenic effects of lysergic acid diethylamide may be due to its effect as a serotonin antimetabolite has been proposed.[1,2] These

(1) D. W. Woolley and E. Shaw, *Brit. Med. J.*, 122–126 (1954).

(2) J. H. Gaddum, Ciba Foundation Symposium, London (1953).



I



II

considerations have been complicated by the observations of Stromberg[3] and Evarts[4] which indicate that bufotenine (II) is itself a hallucinogenic agent.[5] Apparently, in South America the native use of bufotenine, from the plant *piptadenia peregrina*,[3,6] has been in the past as widespread as the peyote cult of the North American West.[7]

To obtain bufotenine and its relatives in quantity for study of their central nervous system effects, a new tryptamine synthesis has been developed which appears to be of wide scope and general application. Giua[8,9] has claimed that oxalyl chloride reacts with indole to give 2-indoleglyoxylyl chloride. A reinvestigation of these apparently neglected studies has disclosed that the beautifully crystalline product, which is obtained in practically quantitative yield, is *3-indoleglyoxylyl chloride.* Giua based his erroneous structure assignment on the observation that 2-indolecarboxylic acid was isolated from a potassium hydroxide fusion of the supposed 2-indoleglyoxylic acid obtained from the acid chloride. Such evidence has been shown to be of doubtful value as a similar alkali fusion led Asahina and Mayeda[10] to incorrect structure proposals for the alkaloids rutaecarpine and evodiamine. As early as 1888 Ciamician *et al.*,[11] observed that skatole gave 2-indolecarboxylic acid (m.p. 203–204) on alkali fusion.

Proof of the position of the glyoxylyl chloride substituent on the indole ring was obtained in an unexpected manner when it was observed in our laboratories that lithium aluminum hydride reduction of the amide obtained from the acid chloride and ammonia yielded *tryptamine* [3-(2-aminoethyl)-indole], while a similar reduction of the ethyl ester of the glyoxylic acid yielded *tryptophol* [3-(2-hydroxyethyl)-indole].[12] Also, a sample of ethyl 3-indoleglyoxylate which was obtained by the method of Oddo and Albanese[13] from indole magnesium iodide and ethyl oxalyl chloride did not depress the melting point (183–185°) of the ester we obtained from the indoleglyoxylyl chloride.

We have found the reaction of oxalyl chloride with indoles offers an attractive approach to a variety of indoleglyoxylic acid derivatives and tryptamines. The reaction has been found to be quite general in application as nicely crystalline glyoxylyl chloride derivatives have been obtained from 2-methylindole, 2-phenylindole, 5,6-dimethoxyindole, 5-acetoxyindole, 5-benzyloxyindole, 6-acetoxy-7-methoxyindole and 1-benz(g)indole. Ethyl 2-indolecarboxylate was unaffected by oxalyl chloride. The excellent yields of amides obtained from the glyoxylyl chlorides together with the facile conversion of the amides to tryptamines in good yield with lithium aluminum hydride have established this route to derivatives of 3-(2-aminoethyl)-indole to be the most convenient of those thus far studied.[14]

This method has been extended to the preparation of the blood serum vasoconstrictor agent serotonin (5-hydroxytryptamine).[15] 5-Benzyloxyindole reacted with oxalyl chloride to give a practically quantitative yield of crude 5-benzyloxy-3-indoleglyoxylyl chloride (m.p. 146–150° dec.). The acid chloride with dibenzylamine gave a 91% yield of 5-benzyloxy-3-indole-N,N-dibenzylglyoxylamide melting at 150–151°. (*Anal.* Calcd. for $C_{31}H_{26}N_2O_3$: C, 78.46; H, 5.52; N, 5.90. Found: C, 78.42; H, 5.52; N, 5.68.)

When this amide was reduced with lithium aluminum hydride 5-benzyloxy-3-(2-dibenzylaminoethyl)-indole was isolated in 92% yield as the hydrochloride salt, melting at 232–233°. (*Anal.* Calcd. for $C_{31}H_{31}ClN_2O$: C, 77.07; H, 6.45; N, 5.80. Found: C, 77.42; H, 6.68; N, 5.73.) This amine was converted to the free base and catalytically debenzylated. The creatinine sulfate complex obtained from the resulting base was identical with the serotonin complex prepared by an earlier method.[16]

For the preparation of bufotenine, 5-benzyloxy-3-indoleglyoxylyl chloride was treated with dimethylamine to obtain 5-benzoyloxy-N,N-dimethyl-3-indoleglyoxylamide, m.p. 178–180.5°. (*Anal.* Calcd. for $C_{19}H_{18}N_2O_3$: C, 70.80; H, 5.62; N, 8.69. Found: C, 70.65; H, 5.41; N, 8.34.) With lithium aluminum hydride the glyoxylamide gave 5-benzyloxy-3-(2-dimethylaminoethyl)-indole which was isolated as the hydrochloride salt, m.p. 154–155°. (*Anal.* Calcd. for $C_{19}H_{23}ClN_2O$: C, 68.96; H, 7.00; N, 8.46. Found: C, 68.97; H, 6.87; N, 8.21.) Debenzylation of the free base obtained from the above hydrochloride salt gave bufotenine base, m.p. 146–147°. The picrate of

(3) V. L. Stromberg, THIS JOURNAL, **76**, 1707 (1954).

(4) E. V. Evarts, Medicinal Chemistry Symposium, Syracuse, N. Y., June, 1954.

(5) Studies by Dr. Nolen Connor of our Laboratories indicate the hydroxyl group is not essential for activity on the central nervous system as 3-(2-dimethylaminoethyl) indole has grossly the same action in the dog as bufotenine. In contrast, 3-(2-methylaminoethyl)-indole has slight activity while 3-(2-*n*-propylaminoethyl)-indole produced no apparent symptoms.

(6) W. E. Safford, *J. Wash. Acad. Sci.*, **6**, 547 (1916).

(7) K. Berlinger, "Der Meskalinraush," Springer, Berlin, 1927.

(8) M. Giua, *Gazz. Chim. ital.*, **54**, 593 (1924).

(9) M. Giua, *Atti, Congr. naz. chim. ind. Milan*, 268 (1924).

(10) Y. Asahina and S. Mayeda, *J. Pharm. Soc. Japan*, **416**, 871 (1916). See also W. O. Kermack, W. H. Perkin, and R. Robinson, *J. Chem. Soc.*, **119**, 1615 (1921).

(11) G. Ciamician and C. Zatti, *Ber.*, **21**, 1929 (1888).

(12) A somewhat similar hydrogenolysis has since been reported by E. Lette and L. Marion, *Can. J. Chem.*, **31**, 775 (1953). These investigators reported the conversion of 3-indolecarboxaldehyde and 3-indole methyl ketone to skatole and 3-ethylindole respectively. A possible mechanism for this conversion is proposed by these workers.

(13) B. Oddo and A. Albanese, *Gazz. chim. ital.*, **57**, 827 (1927).

(14) For a review of tryptamine syntheses see P. L. Julian, E. W. Meyer and H. C. Printy, "Heterocyclic Compounds," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1952, Chapter 1, pp. 51–57; see also J. Thesing and F. Schülde, *Ber.*, **85**, 324–327 (1952); J. Harley Mason and A. H. Jackson, *J. Chem. Soc.*, 1165 (1954).

(15) M. M. Rapport, A. A. Green and I. H. Page, *J. Biol. Chem.*, **176**, 1243 (1948); M. M. Rapport, *ibid.*, **180**, 961 (1949).

(16) M. E. Speeter, R. V. Heinzelman and D. I. Weisblat, THIS JOURNAL, **73**, 5514 (1951).

this base has been shown to be identical to the bufotenine picrate obtained from *piptadenia peregrina*.[3]

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RECEIVED JUNE 14, 1954

CYCLOPENTADIENYL COMPOUNDS OF Sc, Y, La, Ce AND SOME LANTHANIDE ELEMENTS

Sir:

The cyclopentadienyl ring is unusual in the number of metals with which it forms organometallic compounds. This property arises from the fact that the ring may be attached to a metal in three ways: (a) by the two electron covalent bond, which may be referred to as the "sandwich bond," to many transitional metals,[1a,b]; (b) by a covalent bond between a metal and a single carbon atom of the ring. The silicon cyclopentadienyl compounds[2] may be of this type, (c) by ionic bonds.

The ability of electropositive elements to form ionic cyclopentadienyl compounds is of a more general nature than has been realized previously, although compounds such as cyclopentadienylsodium have long been known.[3] The elements scandium, yttrium, lanthanum and the lanthanide elements provide an ideal test case, since no organometallic compounds of these elements have been confirmed.

The anhydrous metal chlorides were stirred with cyclopentadienyl sodium in tetrahydrofuran solution. The solvent was removed and the residues heated at 200–250° in vacuum. Tricyclopentadienyl metal compounds of the formula $(C_5H_5)_3M$, where M may be Sc, Y, La, Ce, Pr, Nd, Sm and Gd, were obtained as sublimates in yields of the order of 65%. Typical analyses are: *Sc*—Found: C, 73.7; H, 6.0; Sc, 18.3; required: C, 74.0; H, 6.2; Sc, 18.5; *Ce*—Found: C, 51.6; H, 4.1; Ce, 42.8; required: C, 53.7; H, 4.5; Ce, 41.8; *Nd*—C, 51.8; H, 4.6; Nd, 41.2; required: C, 53.1; H, 4.5; Nd, 42.5. *Sm*—Found: C, 51.3; H, 4.2; Sm, 43.3; required, C, 52.2; H, 4.3; Sm, 43.5.

The compounds are all crystalline solids, thermally stable to at least 400°, which sublime above 220° at 10^{-4} mm.: *Sc*, straw color, m.p. 240°; *Y*, pale yellow m.p. 295°; *La*, colorless, m.p. 395°; *Ce*, orange, m.p. 435°; *Pr*, pale green, m.p. 420°; *Nd*, pale blue, m.p. 380°; *Sm*, orange, m.p. 365°; *Gd*, pale yellow, m.p. 350°. The compounds decompose with water giving cyclopentadiene and the hydroxide. They are insoluble in hydrocarbon solvents but dissolve readily in tetrahydrofuran and glycol dimethyl ether. They react only slowly with air. Tricyclopentadienylcerium is an exception, in that it is blackened instantaneously by even traces of oxygen; it is also unusual in giving a blue green vapor. The ionic nature of the compounds is indicated by their instantaneous and quantitative reaction with ferrous chloride in tetrahydrofuran solution to give ferrocene. The absorption spectra in tetrahydrofuran show complex and very sharp bands reminiscent of those of the lanthanide ions in aqueous solutions; this resemblance is shown also in their magnetic properties.

The remaining lanthanide elements will probably form similar compounds. In the "actinide" series where similar behavior is to be expected we have prepared a brown dicyclopentadienyl chloro compound of uranium.

In the transitional series we have shown that dicyclopentadienyl manganese[4] is ionic. It has a magnetic moment corresponding to five unpaired electrons when magnetically dilute, and forms conducting solutions in liquid ammonia. The formation of the ionic dicyclopentadienylmanganese, rather than a covalent bis-cyclopentadienylmanganese, must be attributed not to a high electropositive nature of the metal, but to the exceptional stability of the manganous ion, which has the 3d shell half filled. It may be noted, however, that since the negative charge will be distributed over the anion, the most likely packing in the crystal will have the cation between the planes of the rings in a "sandwich" configuration similar to that of ferrocene.[1a]

(1) (a) J. D. Dunitz and L. E. Orgel, *Nature*, **171**, 121 (1953); (b) W. Moffitt, THIS JOURNAL, **76**, 3386 (1954).

(2) K. C. Frisch, *ibid.*, **75**, 6050 (1953).

(3) J. Thiele, *Ber.*, **34**, 68 (1901).

(4) G. Wilkinson and F. A. Cotton, *Chemistry and Industry (London)*, **11**, 307 (1954).

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RECEIVED NOVEMBER 10, 1954

STEROIDS. LXIII.[1] SYNTHESIS OF Δ^4-19-NOR-PREGNENE-11β,17α,21-TRIOL-3,20 DIONE (19-NORHYDROCORTISONE) AND RELATED 19-NOR-ADRENAL HORMONES

Sir:

The observation that removal of the C-19 angular methyl group in the case of progesterone,[2a] desoxycorticosterone[2b] and 17α-ethynyltestosterone[2c] resulted in a marked increase in hormonal activity has encouraged us to undertake the more complicated task of preparing similar derivatives of 11-oxygenated hormones. We should now like to announce the successful synthesis by a combined chemical-biochemical procedure of the 19-nor analog (III) of the most important adrenal hormone Δ^4-pregnene-11β,17α,21-triol-3,20-dione (hydrocortisone or Compound F) and of some related substances.

Alkaline hydrogen peroxide oxidation of 3-hydroxy-17-acetyl-1,3,5,16-estratetraene[3] gave the corresponding 16α,17α-epoxide [m.p. 234–236°, $[\alpha]^{20}D$ +124° (all rotations in $CHCl_3$); found: C, 76.72; H, 7.88] which upon conversion to the 3-methyl ether (m.p. 141–144°) followed by hydrogen bromide opening, catalytic debromination to 3-methoxy-17α-hydroxy-17-acetyl-1,3,5-estratriene

(1) Paper LXII, F. Sondheimer, M. Velasco and G. Rosenkranz, THIS JOURNAL, in press.

(2) (a) C. Djerassi, L. Miramontes and G. Rosenkranz, *ibid.*, **75**, 440 (1953); (b) A. Sandoval, L. Miramontes, G. Rosenkranz, C. Djerassi and F. Sondheimer, *ibid.*, **75**, 4117 (1953); (c) C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, *ibid.*, **76**, 4092 (1954).

(3) C. Djerassi, G. Rosenkranz, J. Iriarte, J. Berlin and J. Romo, *ibid.*, **73**, 1523 (1951).