further elaboration by Haszeldine.[3] We find their criticism well founded and accept it. We also offer new experimental evidence confirming their view that the condensation places the CF_2, rather than the CFCl group in the middle.

On the experimental preparation of C_3F_6ClI or $C_3F_3Cl_4Br$ we all agree. As to the direction of addition, *i.e.*, the distinction between CF_3–$CFCl$–CF_2I or CF_3–CF_2–$CFClI$, and between CCl_3–$CFCl$–CF_2Br or CCl_3–CF_2–$CFClBr$, we based our original interpretation on the assumption that a conventional zinc in alcohol reaction would create an olefin without loss of organic fluorine in the first alternative, but would remove some fluorine in the second alternative if it reacted at all. Since, experimentally, no organic fluorine was lost, the first alternative was adopted. However, as soon as Miller showed that the zinc reaction was not restricted to the creation of a double bond, and could cause the formation of an organo-zinc compound, our assumption became inadequate, and our conclusion unsupported.

The action of zinc on $C_3F_3Cl_4Br$ was reinvestigated by a new procedure.[4] In solution in acetic anhydride, $C_3F_3Cl_4Br$ reacts very rapidly with zinc, and if the reaction is moderated by means of methylene chloride as an internal cooling agent (reflux at 40°), most of the reagent is transformed into crystalline $C_6F_6Cl_8$, m.p. 40° [*Anal.* F, 24.1; Cl, 59.6. Calcd.: F, 24.2; Cl, 60.4], and the balance of the reagent recovered intact. The zinc consumed is accounted for as zinc bromide only; there is no fluorine ion to be detected.

The C_6-compound can be either $(CCl_3$–$CFCl$–CF_2–$)_2$ or else $(CCl_3$–CF_2–$CFCl$–$)_2$ and therefore it does not solve the problem of the original direction of condensation between CCl_3Br and CF_2=$CFCl$. However, the first alternative should react quite easily with zinc and alcohol in a conventional reaction, to give a diene, CCl_2=CF—CF_2—CF_2—CF=CCl_2, while the second alternative should react much more sluggishly to give the monoölefin, CCl_3—CF_2—CF=CF—CF_2—CCl_3. Actually, the conventional zinc dehalogenation did not proceed noticeably below 110°, and it gave, quantitatively, a single product $C_6F_6Cl_6$. [*Anal.* F, 28.0; Cl, 52.2; F/Cl, 0.536. Calcd.: F, 28.6; Cl, 53.4; F/Cl, 0.536.] A diene $C_6F_6Cl_4$ would have required 34.8, 43.2 and 0.806, respectively.

The C_6-paraffin was therefore written CCl_3-$CF_2CFClCFClCF_2CCl_3$, obtained from two moles of CCl_3–CF_2–$CFClBr$. We are thus accepting and experimentally confirming the direction of free radical addition to CF_2=$CFCl$ proposed by our critics.

Experimental

One volume of $C_3F_3Cl_4Br$ (86 g. or 0.27 mole), zinc (17.7 g. or 0.27 atom), 3 volumes of CH_2Cl_2 and 2 volumes of acetic anhydride were stirred for six hours. The unused zinc amounted to 2.9 g. (0.044 atom), indicating a consumption of 14.8 g. (0.227 atom). Redistillation recovered 8.1 g. of $C_3F_3Cl_4Br$ (0.026 mole). Solid $C_6F_6Cl_6$ melting about 40° amounted to 60 g. (0.11 mole), which accounted for 0.22 mole of original $C_3F_3Cl_4Br$; this is an 81.5% yield and a 91% recovery of organic material.

$C_6F_6Cl_6$ did not react noticeably with zinc in boiling ethanol. A metal container was then loaded with $C_6F_6Cl_8$ (43 g. or 0.092 mole), zinc (6 g. or 0.092 atom) and 200 cc. of ethanol, and it was rocked at 110° for six hours. The working up gave 19 g. (0.049 mole) of $C_6F_6Cl_8$, d^{28}_4 1.8126, $n^{28}D$ 1.4501, MR 59.1, AR_F 1.2, and 16.5 g. (0.035 mole) of recovered $C_6F_6Cl_8$; this is a 52% yield and 90% recovery of organic material. In confirmation 2.7 g. (0.041 atom) of zinc was recovered, showing a consumption of 3.3 g. (0.051 atom).

DEPARTMENT OF CHEMISTRY
THE OHIO STATE UNIVERSITY
COLUMBUS 10, OHIO

(3) R. N. Haszeldine and B. R. Steele, *J. Chem. Soc.*, 1592 (1953).
(4) A. L. Henne, THIS JOURNAL, **75**, 5750 (1953).

Preparation and Properties of Some New Chelating Agents[1]

BY E. G. KOVACH AND D. E. BARNES

RECEIVED OCTOBER 30, 1953

In conjunction with work being carried out in these laboratories on the mode of action of fungicides we wish to report the synthesis of two new compounds with chelating properties prepared as potential fungistatic agents. As an analog of the well-known 8-hydroxyquinoline we have prepared 7-indiazolol (VI), and as an analog of Cupferron we have prepared ammonium N-2-pyridyl-N-nitrosohydroxylamine (Pyridine Cupferron), replacing the phenyl group by a 2-pyridyl radical.

TABLE I

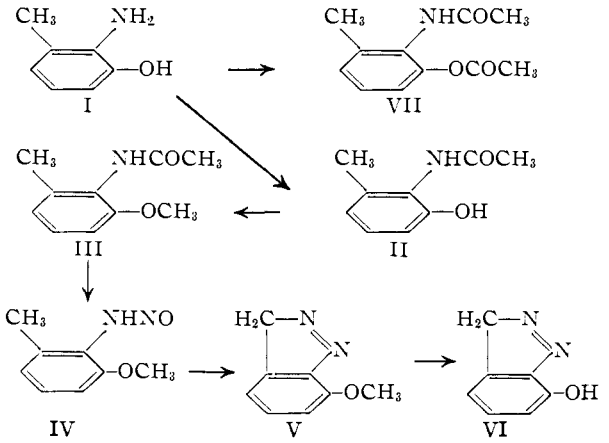
PRECIPITATING PROPERTIES AND FUNGITOXICITY OF 7-INDIAZOLOL AND AMMONIUM N-2-PYRIDYL-N-NITROSOHYDROXYLAMINE

	7-Indiazolol	Pyridine Cupferron
Maley–Mellor metals		
Cu^{++}	+ (purple)	+ (green)
Pb^{++}	+ (white)	+ (white)
Cd^{++}	+ (white)	+ (white)
Fe^{++}	+ (black)	+ (red)
Co^{++}	+ (rose)	− (intense red color)
Zn^{++}	+ (white)	−
Ni^{++}	+ (blue-gray)	−
Mn^{++}	−	−
Mg^{++}	−	−
Monovalent metals		
Ag^{+}	+ (white)	+ (white)
Divalent metals		
Hg^{++}	−	+ (yellow-white)
Sn^{++}	−	+ (white)
Ca^{++}	−	+ (white)
Ba^{++}	−	−
Sr^{++}	−	−
Trivalent metals		
Cr^{+++}	−	−
Bi^{+++}	−	−
Al^{+++}	−	−
Percentage inhibition of growth of *A. niger* at concn. of		
10^{-3} *M*	27	16
10^{-4} *M*	8	3
10^{-5} *M*	4	1

(1) This work was done for the Engineering Research and Development Laboratories, Fort Belvoir, Va., under Contract DA-44-009 eng-690, and is published with their permission.

The fungitoxicity and the chelating powers of these compounds against a series of metallic ions are shown in Table I.

The 7-indiazolol (VI) was prepared through N-acetylation of 2-amino-3-methylphenol (I), followed by methylation, nitrosation, condensation and demethylation.



Direct condensation of I to VI in acetic anhydride, acetic acid or dry benzene was attempted, according to the classic report of Noelting on the preparation of substituted indazoles[2] and the more recent work of Barclay, Campbell and Dodds[3] and of Stephenson.[4] All trials gave negative results, probably due to inner salt formation between the adjacent phenolic and amino groups in I. The action of diazomethane on I yielded only starting material. Acetylation with acetic anhydride and sodium acetate produced the new diacetate VII in good yield, but the instability of indazoles toward alkali indicated that hydrolysis of the acetate ester subsequent to ring closure would probably cleave the heterocyclic ring; therefore this path was discarded. The method diagrammed gave the desired compound in reasonable yield.

Experimental

All melting points are uncorrected.

7-Indiazolol. N-Acetyl-2-amino-3-methylphenol (II).[5]—One hundred and fifty grams of 2-amino-3-methylphenol[6] was treated in three batches as follows: Fifty grams of the aminocresol was dissolved in 445 ml. of 1.0 *N* HCl and 65 g. of acetic anhydride. To this was added 260 ml. of a saturated aqueous solution of sodium acetate, and the stoppered flask was shaken vigorously. After a few minutes a tan precipitate formed. Removal by filtration, washing with water, and drying in air gave a total yield of 145 g. (72%). The melting point was 160–161°.

Anal. Calcd. for $C_9H_{11}O_2N$: N, 8.48. Found: N, 8.22.

Diacetate of 2-Amino-3-methylphenol (VII).—Four grams of 2-amino-3-methylphenol was refluxed for seven hours in 30 ml. of acetic anhydride containing 1 g. of anhydrous sodium acetate. The solvent was removed *in vacuo*, and the residue taken up in 200 ml. of dry ether. After filtering, the solution was concentrated on the steam-bath and treated with an equal amount of petroleum ether (30–40°). Cooling and slow evaporation yielded fine white crystals, m.p. 81–82°.

Anal. Calcd. for $C_{11}H_{13}O_3N$: N, 6.76. Found: N, 7.01.

N-Acetyl-2-amino-3-methylanisole (III).[7]—One hundred and forty-five grams of the N-acetyl derivative (above) was dissolved in 870 ml. of 1.0 *N* KOH (containing 49.3 g., 1 equiv. KOH) and treated with 81.2 ml. of dimethyl sulfate (111 g., 1 equiv.), and the stoppered flask was shaken vigorously. Some heat was generated, and the contents of the flask darkened. After about ten minutes of shaking and chilling in an ice-bath, the methoxy derivative was filtered off, washed with water and air-dried. The yield was 121 g. (74.5%). After recrystallization from petroleum ether (90–100°) and benzene it had a melting point of 123°.

Anal. Calcd. for $C_{10}H_{13}O_2N$: N, 7.82. Found: N, 7.46.

N-Nitroso-2-amino-3-methylanisole (IV).—One hundred and ten grams of N-acetyl-2-amino-3-methylanisole was treated in eleven batches in the following manner: Ten grams of the material was dissolved in a mixture of 200 ml. of glacial acetic acid and 80 ml. of concd. HCl. This solution was cooled to 0° or lower and treated with a solution of 10 g. of sodium nitrite in 75 ml. of water. The stoppered flask was left in an ice–salt mixture for at least one hour. The solution was then diluted with *ca.* 500 ml. of water and left standing in the refrigerator for 3–4 hours. A crystalline yellow precipitate slowly appeared. At the end of this time the precipitate was separated by filtration, washed well with ice-water and dried *in vacuo* over concd. H_2SO_4. The yield of N-nitroso-2-amino-3-methylanisole was 62 g. (56%) with a melting point of 72–74°. This material decomposes slowly when kept at room temperature for several days.

Anal. Calcd. for $C_8H_{10}O_2N_2$: N, 16.86. Found: N, 16.33.

7-Methoxyindiazole (V).—Sixty-two grams of N-nitroso-2-amino-3-methylanisole was dissolved in *ca.* 400 ml. of sodium-dried benzene and allowed to stand for 24 hours. After this time the dark red solution was refluxed for one hour, and then about half the benzene was distilled off. The remaining solution was washed with 1 *N* Na_2CO_3 solution, and next with water, and was then extracted three times with 2 *N* HCl. The combined acid extracts were chilled and made alkaline with 2 *N* NaOH, whereupon 7-methoxyindiazole precipitated out. The yield was 23 g. (41.5%), and the melting point was 91–92°.

Anal. Calcd. for $C_8H_8ON_2$: N, 18.92. Found: N, 18.45.

7-Indiazolol (VI).—Twenty-three grams of the 7-methoxyindiazole was dissolved in *ca.* 200 ml. of HI (d. 1.5) and heated under reflux for 3 hours. The solution was chilled and carefully adjusted to *p*H 7 with 2 *N* NaOH, at which point precipitation of the amphoteric 7-indiazolol was at a maximum. The tan product weighed 18 g. (86% yield), and the melting point was 135.5–136.5°. Hot water was found to be the best solvent for recrystallization, but better purification is accomplished by high vacuum sublimation. The material darkens somewhat on standing.

Anal. Calcd. for $C_7H_6N_2O$: C, 62.67; H, 4.51; N, 20.89. Found: C, 62.91; H, 4.39; N, 20.11.

Pyridine Cupferron. N-2-Pyridylhydroxylamine.[8]—A bomb of 770 ml. total internal capacity was charged with *ca.* 1 g. of PtO_2 in 30 ml. of ethanol, and this was completely reduced by charging the bomb to *ca.* 50 p.s.i. with hydrogen and rocking for 15 minutes at room temperature. The bomb was then opened and charged with 10 g. of 2-nitropyridine[9] in 140 ml. of ethanol. This left a volume of 600 ml. which contained the calculated amount of hydrogen for reduction

(2) E. Noelting, *Ber.*, **37**, 2256 (1904).

(3) I. M. Barclay, N. Campbell and G. Dodds, *J. Chem. Soc.*, 113 (1941).

(4) E. F. M. Stephenson, *Org. Syntheses*, **29**, 54 (1949).

(5) A. Proskouriakoff and R. J. Titherington, THIS JOURNAL, **52**, 3982 (1930).

(6) H. H. Hodgson and H. G. Beard, *J. Chem. Soc.*, **127**, 498 (1925).

(7) M. Heidelberger and W. A. Jacobs, THIS JOURNAL, **41**, 1453 (1919).

(8) This catalytic hydrogenation was reported on a semi-micro scale by G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 113 (1949). They point out the necessity of avoiding excessive hydrogenation because of the easy further reduction to 2-aminopyridine. They did not isolate the solid hydroxylamine, identifying it merely by derivatives, but when we repeated their work the same crystalline residue was noted upon removal of the solvent.

(9) Made by oxidation of 2-aminopyridine with fuming sulfuric acid and 30% H_2O_2 according to the method of A. Kirpal and W. Bohm, *Ber.*, **65**, 680 (1932). These authors suggest recrystallization from ethanol–water; better results were obtained by collecting the product from a partially evaporated ether solution. The 2-nitropyridine forms almost white crystals, m.p. 70–71°. The highest yield obtained in several runs was over 98%. The average yield was 70–75%.

of $-NO_2$ to $-NHOH$ when charged to 99 p.s.i. The bomb was rocked for one hour, and reduction was shown to be complete by the absence of any internal pressure when the bomb was opened. The catalyst was removed by filtration, and removal of the solvent *in vacuo* at or below room temperature yielded a copious crystalline residue of N-2-pyridylhydroxylamine which reduced Tollens reagent immediately. This material was used in the next step without purification.

Ammonium Salt of N-2-Pyridyl-N-nitrosohydroxylamine.—The above residue was taken up in 200 ml. of ether and cooled to −5°. Gaseous ammonia was bubbled into the solution for several minutes, and then ethyl nitrite (prepared by the action of 1:1 HCl on 50 g. of $NaNO_2$ in 80 ml. of 95% ethanol) was concurrently introduced. The solution soon turned a very dark brown, and after a few minutes a cream-white precipitate appeared. This was filtered off and dried in a stream of ammonia. Further treatment of the filtrate with ammonia yielded additional product, which was again removed. Finally the solution was resaturated with ammonia and left in the refrigerator overnight. The following day additional product was removed; this time lag in precipitation has been noted with several Cupferron derivatives whose preparation will be reported later. The combined yield was 9.8 g. (78% over-all from 2-nitropyridine). Recrystallized from ethanol (soluble) and ether (insoluble), the material had a melting point of 133–135° dec.

Anal. Calcd. for $C_5H_8O_2N_4$: C, 38.46; H, 5.17; N, 35.88. Found: C, 38.69; H, 5.32; N, 35.35.

Precipitation Tests.—The metallic salts were employed in the form of sulfates (Al^{+++}, Fe^{++}), chlorides (Sn^{++}, Mn^{++}), nitrates (Bi^{+++}, Ag^{+}, Ni^{++}) and acetates (all the rest). One milliliter of a stock solution 0.02 *M* in metallic ion was treated with 4 ml. of 0.01 *M* chelating agent (water was used to dissolve the Pyridine Cupferron and 50% ethanol to dissolve the 7-indiazolol). Only those mixtures which gave precipitates within five minutes were graded as positive. It was noted that several mixtures gave precipitates after standing for 12 or even 48 hours.

Toxicity Tests.[10]—The toxicity of these substances toward *A. niger* was determined by means of the standard P.D.C. Agar Plate Test.[11]

(10) We are happy to acknowledge the assistance of Dr. S. S. Block, of our Chemical Engineering Staff, in obtaining the fungitoxicity data.

(11) Prevention of Deterioration Center, National Research Council, Dec., 1948.

DEPARTMENT OF CHEMISTRY AND DEPARTMENT OF CHEMICAL ENGINEERING
UNIVERSITY OF FLORIDA
GAINESVILLE, FLORIDA

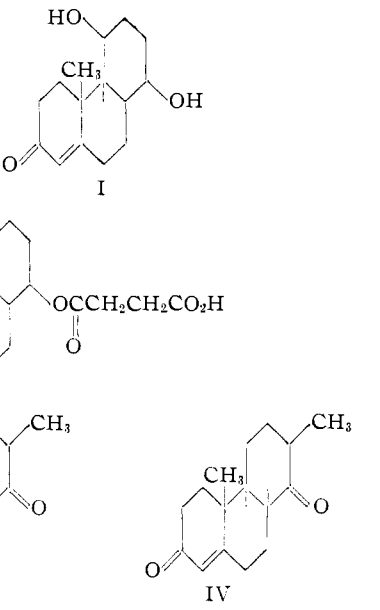
Some Optically Active Dodecahydrophenanthrenes[1]

BY R. M. LUKES AND L. H. SARETT

RECEIVED OCTOBER 14, 1953

During the course of our total synthesis of cortisone,[2] the possibility of optical resolution was investigated at various intermediate stages. One compound which proved to be readily separable into optical antipodes was the tricyclic dihydroxyketone I.[3] The 1-monohemisuccinate (II) afforded a brucine salt which after two crystallizations had a constant rotation. Alkaline hydrolysis of this salt gave an over-all yield of 45% of the theoretical amount of (−)-I.

Some of the transformations that have been described in detail for racemic I[3] were applied to (−)-I with the idea of investigating some of the relationships of optical rotation to structure in this series. The products obtained are listed in Tables I and II.



The shift in molecular rotation (hereafter referred to as ΔM_D) for the conversion of a Δ^5-3β-hydroxysteroid to a Δ^4-3-ketosteroid has been found to be approximately +511°.[4] That perhydrophenanthrenes such as are described in this paper would be expected to show a comparable positive ΔM_D for the same transformation is demonstrated by the oxidation of the Köster–Logemann ketone III to the dione IV with its attendant ΔM_D of +472°.[5] Similarly, the hydrolysis of the Δ^5-3-ethylenedioxy derivatives of cholestenone,[6] 11-ketoprogesterone[7] and cortisone[8] to the parent Δ^4-3-ketosteroids results in positive ΔM_D values of +562°, +565° and +454°, respectively. However, when the *anti–trans* compounds (3) and (4) in Table II are converted to compounds (6) and (5) in Table I, respectively, *negative* ΔM_D values of −670° and −892° are obtained.[9] Thus it is evident that the tricyclic series presented in this paper is enantiomorphic to the steroids.

If one goes on and compares the ΔM_D values for the large variety of interconversions possible among the compounds in Tables I and II, it becomes immediately evident that there is a remarkable lack of consistency, and that the ΔM_D values are not predictable, and difficult to rationalize. The inevitable conclusion is that large and seemingly irregular vicinal effects, not unexpected in a series of three, four or five contiguous asymmetric centers, influence the rotatory contributions of those centers to such an extent as to make the

(1) Paper IX in the series "Approaches to the Total Synthesis of Adrenal Steroids."

(2) L. H. Sarett, G. E. Arth, R. M. Lukes, R. E. Beyler, G. I. Poos, W. F. Johns and J. M. Constantin, THIS JOURNAL, **74**, 4974 (1952).

(3) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *ibid.*, **75**, 422 (1953).

(4) D. H. R. Barton and W. Klyne, *Chemistry and Industry*, **67**, 755 (1948).

(5) H. Köster and W. Logemann, *Ber.*, **73**, 298 (1940).

(6) E. Fernholz and H. E. Stavely, Abstracts, 102nd Meeting of the Am. Chem. Soc., Atlantic City, N. J., 39M (1941).

(7) J. M. Constantin, A. C. Haven, Jr., and L. H. Sarett, THIS JOURNAL, **75**, 1716 (1953).

(8) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953).

(9) The comparison is restricted to those pairs having the *anti-trans* configuration of C-4b, C-4a, and C-10a.