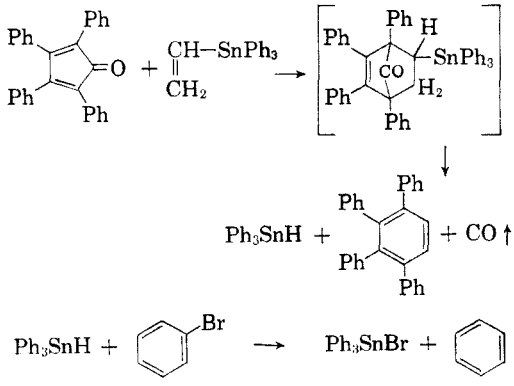
Communications TO THE EDITOR

Hydrogenolysis of Bromobenzene with Triphenyltin Hydride

Sir:

In attempting to prepare organometallic compounds *via* the Diels-Alder reaction, the reaction of tetracyclone (tetraphenylcyclopentadienone) with triphenylvinyltin in refluxing bromobenzene was examined. Among the products isolate were tetraphenyltin, m.p. 228–229° (reported:[1] 229.2°), 1,2,3,4-tetraphenylbenzene (I), m.p. 192.5–193.5° (reported:[2] 193–194°), 2,3,4,5-tetraphenylcyclopent-2-enone, m.p. 160–162° (reported:[3] 160–162° and 162–163°), and triphenyltin bromide (II), m.p. 121.5–122.5° (reported:[4] 121–122°)—all well-known compounds. A reducing gas was evolved throughout the course of the reaction. When tetracyclone was omitted from the boiling bromobenzene solution, tetraphenyltin was isolated, but no triphenyltin bromide.

To rationalize the appearance of these products, it was assumed that tetracyclone underwent the Diels-Alder reaction with triphenylvinyltin affording a transient adduct which eliminated carbon monoxide (the reducing gas?) and triphenyltin hydride to give fully aromatic I. The triphenyltin hydride then reacted with bromobenzene to give II and benzene.



To test this assumption a solution of triphenyltin hydride in bromobenzene was refluxed and afforded II in yields of 61–72% and benzene in yields of 60–75%.

This first example of the hydrogenolysis of an aromatic bromide with triphenyltin hydride is important in view of the recently reported hydrogenolyses of allyl bromide[5] and saturated bromides.[6,7] We have also determined that iodobenzene reacts more rapidly than bromobenzene and that chlorobenzene is least reactive.

Additional work to outline the scope of the hydrogenolysis of aromatic halogen is under way.

Acknowledgment. We are glad to thank the Metal and Thermit Corp. for the gift of generous supplies of triphenylvinyltin and triphenyltin chloride.

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(1) H. D. K. Drew and J. K. Landquist, *J. Chem. Soc.*, 1480 (1935).

(2) W. Dilthey and G. Hurtig, *Ber.*, **67B**, 495 (1934).

(3) N. O. V. Sonntag, S. Linder, E. I. Becker, and P. E. Spoerri, *J. Am. Chem. Soc.*, **75**, 2283 (1953).

(4) O. H. Johnson and J. R. Holum, *J. Org. Chem.*, **23**, 738 (1958).

(5) G. J. M. van der Kerk, J. G. Noltes, and J. G. A. Luijten, *J. Appl. Chem. (London)*, **7**, 356 (1957).

(6) G. J. M. van der Kerk, J. G. A. Luijten, and J. G. Noltes, *Angew. Chem.*, **70**, 298 (1958).

(7) After this Communication had been submitted, we found that J. G. Noltes and G. J. M. van der Kerk in the course of their extensive investigation of organotin chemistry independently discovered the hydrogenolysis of bromobenzene with triphenyltin hydride in 54% yield. See "Functionally Substituted Organotin Compounds," report to the Tin Research Institute, June, 1958.

A New Potent Synthetic Analgesic

Sir:

The substitution of phenethyl for methyl on the nitrogen of several well known analgesics has generally produced a marked increase in potency.[1] Well established also is the fact that one optical isomer (usually *levo*) of a racemate contains. with few exceptions, practically all of the analgesic activity.[2] Accordingly, we have synthesized (±)-2′-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan (II) and its optical isomers from (±)-2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (I) (an effective analgesic in mice)[3] by a route previously described.[4] Acetylation of I with acetic anhydride gave the crude *O*-acetyl derivative

(1) J. Weijlard, P. D. Orahovats, A. P. Sullivan, Jr., G. Purdue, F. K. Heath, and K. Pfister, 3rd, *J. Am. Chem. Soc.*, **78**, 2342 (1956); T. D. Perrine and N. B. Eddy, *J. Org. Chem.*, **21**, 125 (1956); A. Grüssner, J. Hellerbach, and O. Schnider, *Helv. Chim. Acta*, **40**, 1232 (1957); L. F. Small, N. B. Eddy, J. H. Ager, and E. L. May, *J. Org. Chem.*, **23**, 1387 (1958).

(2) O. J. Braenden, N. B. Eddy, and H. Halbach, *Bull. World Health Organization*, **13**, 937 (1955).

(3) This compound is comparable to morphine in analygesic effectiveness, E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957).

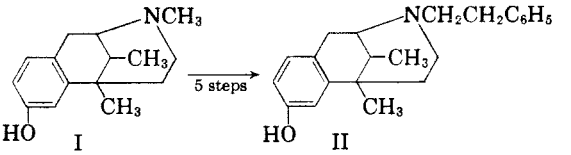
(4) E. L. May, *J. Org. Chem.*, **21**, 899 (1956).

which was *N*-demethylated by the method of von Braun.[5] Phenylacetylation of the resultant secondary amine produced the amide which, on reduction with ethereal lithium aluminum hydride, yielded (±)-2'-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan (II) isolated as the *hydrobromide* salt, m.p. 166–170°[6] (*Anal.* Calcd. for $C_{22}H_{28}BrNO$: C, 65.68; H, 7.01. Found: C, 65.40; H, 7.00). The free *base* (*Anal.* Calcd. for $C_{22}H_{27}NO$: C, 82.20; H, 8.47. Found: C, 82.27; H, 8.48) melted at 180–181°.

Treatment of the hydrochloride salt of I in water with (±)-α-bromocamphor-π-sulfonic acid [(+)-3-bromo-8-camphorsulfonic acid] ammonium salt[7] gave, after fractional crystallization of the diastereoisomeric salts and neutralization of these salts with aqueous ammonium hydroxide, (−)-I, m.p. 183–184.5°, $[\alpha]_D^{20}$ −84.8° (*c*, 0.92, abs. alcohol) (*Anal.* Calcd. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 77.91; H, 8.97); *hydrobromide*, m.p. 238–241°, $[\alpha]_D^{20}$ −52.0 (*c*, 2.00, water) (*Anal.* Calcd. for $C_{15}H_{22}BrNO$: C, 57.68; H, 7.10. Found: C, 57.66; H, 7.34) and (+) -I, m.p. 183–184.5°, $[\alpha]_D^{20}$ +84.3 (*c*, 0.83, abs. alcohol) (*Anal.* Calcd. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 77.75; H, 9.25); hydrobromide, m.p. 238–242°, $[\alpha]_D^{20}$ +52.1° (*c*, 1.46, water) (*Anal.* Calcd. for $C_{15}H_{22}BrNO$: C, 57.68; H, 7.10. Found: C, 57.93; H, 7.18).

As described in the preparation of (±) - II, (−)-I and (+)-I gave, respectively, (−)-II *hydrobromide*, m.p. 284–287°, $[\alpha]_D^{20}$ −84.1° (*c*, 1.12, 95% ethanol) (*Anal.* Calcd. for $C_{22}H_{28}BrNO$: C, 65.68; H, 7.01. Found: C, 65.82; H, 7.02); base, m.p. 159–159.5°, $[\alpha]_D^{20}$ =121.6° (*c*, 0.74, 95% ethanol) (*Anal.* Calcd. for $C_{22}H_{27}NO$: C, 82.20; H, 8.47. Found: C, 81.95; N, 8.44) and (+)-II *hydrobromide*, m.p. 284–287°, $[\alpha]_D^{20}$ +84.4° (*c*, 1.47, 95% ethanol) (*Anal.* Calcd. for $C_{22}H_{28}BrNO$: C, 65.68; H, 7.01. Found: C, 65.65; H, 7.15); *base* m.p. 159–160°, $[\alpha]_D^{20}$ +120° (*c*, 0.60, 95% ethanol) (*Anal.* Calcd. for $C_{22}H_{27}NO$: C, 82.20; H, 8.47. Found: C, 82.35; H, 8.41).

In mice (subcutaneous administration) (−)-2'-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (I) proved to be almost twice as effective (ED_{50} 1.7 mg./kg.) and less than half as toxic (LD_{50}>400 mg./kg.) as (+)-I while the *dextro*-isomer was inactive at 20 mg./kg., a convulsant dose. The (−)-2'-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan (II) (ED_{50} 0.11 mg./kg.) is 12–15 times more potent than (−)-I, almost 20 times more so than morphine. The (+) -II is also surprisingly effective (ED_{50} 6.7). Finally (±)-II (ED_{50} 0.25) has shown low physical dependence potency in the monkey.[8] Addiction studies in man[9] are in progress. Initial clinical experiments[10] with this racemate show it to be a promising agent for the relief of both acute and chronic pain.



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(5) J. von Braun, O. Kruber, and E. Aust, *Ber.*, **47**, 2312 (1914).

(6) After about a year the melting point had risen to 247–250°. Analysis and infrared data proved the new crystals to be another crystalline modification of II.

(7) From the Aldrich Chemical Co., Inc.

(8) G. Deneau, personal communication.

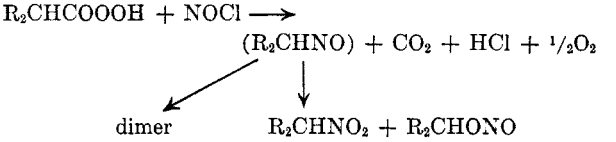
(9) Research Addiction Center, National Institute of Mental Health, Lexington, Ky.

(10) Large-scale preparation of this compound and clinical studies are due to the Smith Kline & French Laboratories, Philadelphia.

A New Reaction of Organic Peroxyacids

Sir:

If a primary or secondary peroxyacid is allowed to react with a nitrosating agent in an appropriate solvent in the cold, an instantaneous reaction occurs. The solution becomes deep blue or green, colors characteristic of monomeric C-nitroso compounds. Upon working up the crude products bis-nitroso compounds have been isolated, as well as nitro compounds and nitrite esters. The following equation approximates the reaction:



We will illustrate it by the results obtained in a typical experiment with peroxyphenylacetic acid.

Peroxyphenylacetic acid (12 g.) prepared by a modification of the method of Swern and coworkers[1] (purity by titration for active oxygen 95%, m.p. 76–77°), was allowed to react with nitrosyl chloride in petroleum ether at 0°; the solution became deep green in color. Three products were isolated from the reaction mixture: (a) bis-α-nitrosotoluene, an ether-insoluble solid, m.p. 120–121.5[2,3]; crude yield 0.7 g. λ_{max} 295 mμ, lit. 296 mμ.[3] *Anal.* Found C, 69.23; H, 5.83; N, 11.46. The infrared spectrum showed a strong peak at 8.53μ in chloroform and 8.55μ in a Nujol mull (lit.[3] 8.58μ), and the absence of the 6.25 and 6.45μ

(1) W. E. Parker, C. Ricciuti, C. L. Ogg, and D. Swern, *J. Am. Chem. Soc.*, **77**, 4037 (1955).

(2) R. Behrend and E. König, *Ber.*, **23**, 1776 (1890); *Ann.*, **263**, 210 (1891).

(3) E. Müller and H. Metzger, *Chem. Ber.*, **88**, 165 (1955).