the present work and previous studies of bridgehead silicon, will be dealt with at length in a later full article.

We thank Dow Corning Corporation for continued generous support.

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STEREOSPECIFICITY IN A NEW TYPE OF SYNTHETIC ANTITUBERCULOUS AGENT[1,2]

Sir:

We wish to report the synthesis of a new highly-active antituberculous compound, the dextrorotatory form of 2,2′-(ethylenediimino)-di-1-butanol (ethambutol),[3] which is four times as active as streptomycin against an established infection with the human strain of *Mycobacterium tuberculosis* in mice. It is also fully active against isoniazid-resistant infections as well as against streptomycin-resistant infections in mice. The sharp stereospecificity of the activity of this synthetic chemotherapeutic agent (*dextro* = 12 × *meso* = >200 × *levo*) contrasts with the equality in acute toxicity of the stereoisomers in mice. The high efficacy index (ratio of tolerance to potency) of this compound has warranted its clinical trial, the results of which will be reported elsewhere.

The experimental chemotherapeutic study of the stereoisomers of 2,2′-(ethylenediimino)-di-1-butanol in comparison with streptomycin and isoniazid is summarized in the table. The antituberculous activity of these isomers varied considerably with the configuration at the asymmetric carbons, the *levo* isomer being inactive at the maximum tolerated dose (at least a 200-fold difference in activity). The one center with the dextrorotatory configuration in the *meso* isomer appears to be the source of its activity even though it is considerably less than half as active as the *dextro* form, both *in vivo* and *in vitro*. In contrast, the acute lethal toxicity in mice of the three isomers and the racemate is the same within experimental error. The reason for the remarkable stereospecificity in this synthetic antibacterial agent is under study. (+)-2,2′-(Ethylenediimino)-di-1-butanol showed no activity against lethal infections with Gram-negative and Gram-positive organisms in mice. The high antibacterial specificity also was confirmed by the lack of activity *in vitro* against these organisms or against various fungi.

(+)-2,2′-(Ethylenediimino)-di-1-butanol also was highly effective using delayed treatment of an established mycobacterial infection of mice. In addition, the activity against infections with mycobacteria resistant to current drugs has been demonstrated clearly. Against a lethal infection in mice with a human strain resistant to the maximum tolerated dose of streptomycin, this new agent was fully as active parenterally as against the strains sensitive to this drug. The same was true of oral treatment in a lethal infection with a bovine strain resistant to the maximum tolerated dose of isoniazid. Equally important is the fact that repeated growth *in vitro* in its presence has failed so far to show the development of resistance to this substance by the human strain of *Mycobacterium tuberculosis*, H37R$_v$.

CHEMOTHERAPEUTIC EVALUATION OF STEREOISOMERS OF 2,2′-(ETHYLENEDIIMINO)-DI-1-BUTANOL·2HCl

	Oral treatment[a]			Subcutaneous treatment[a]		
	ED_{50}[b]	Max. tol. dose[c]	Efficacy index[d]	ED_{50}[b]	Max. tol. dose[c]	Efficacy index[d]
(−)-Isomer	Inactive[e]	6400		Inactive[e]	800	
meso Form	500	6400		500	800	
(±)-Form	90	6400		90	800	
(+)-Isomer	45	6400	120	45	800	18
Streptomycin				80	400	5
Isoniazid	1.2	100	80			

[a] Administration by daily single dosage. [b] Estimated median effective dose (in mg./kg./day administered for 14 days from day of infection) required for 60 day survival where all infected untreated control mice died in an average time of 17 days. The infecting organism was the human strain of *Mycobacterium tuberculosis*, H37R$_v$. [c] The maximum tolerated dose is the amount in mg./kg./day administered for 14 days which gave about 10% weight loss after one week. [d] Ratio of maximum tolerated dose to median effective dose. [e] Inactive at the maximum tolerated dose.

The highly active (+)-isomer was prepared by brief heating of ethylene dichloride with excess (+)-2-amino-1-butanol.[4] A 42% yield of purified (+)-2,2′-(ethylenediimino)-di-1-butanol (m.p. base[5] 87.5–88.8°, m.p. dihydrochloride[6] 198.5–200.3°) was obtained after removal of the less soluble *meso* isomer (m.p. base 135.8–136.5°; m.p. dihydrochloride 203.5–204.6°) corresponding to approximately the amount of *levo* impurity in the (+)-2-amino-1-butanol. The *levo* diamine (m.p. base[7] 89–90°; m.p. dihydrochloride[8] 200.5–201.5°) was prepared in the same way from (−)-2-amino-1-butanol[4] in 52% yield. When (±)-2-aminobutanol reacted with either ethylene chloride, ethylene bromide or ditosyl glycol, the condensation occurred most rapidly at the temperature obtained without solvent, although a longer time at lower temperature (alcohol) has given comparable results. The main products, each isolated in about 40% yield, are the racemic base (m.p. 75–76°; b.p. 160–170° (0.3 mm.); dihydrochloride m.p. 179–180°) and the *meso* diamine. These were separated readily as a result of the low solubility of the latter in a number of solvents. The racemic and *meso* isomers of β,β′-diethyl-1,4-piperazine-

(1) Additional data will be published by Thomas, Baughn, Wilkinson and Shepherd, *Am. Rev. Resp. Dis.*, 1961.

(2) We wish to acknowledge the valuable assistance of Drs. S. Kushner and H. J. White of these Laboratories.

(3) Ethambutol is the generic name reserved for this isomer by the Lederle Laboratories Division of the American Cyanamid Company.

(4) From commercial (±)-2-aminobutanol by the tartrate resolution procedure of F. H. Radke, R. B. Fearing and S. W. Fox, *J. Am. Chem. Soc.*, **76**, 2801 (1954).

(5) *Anal.* Calcd.: 58.8% C, 11.8% H, 13.7% N. Found: 58.8% C, 12.1% H, 13.7% N.

(6) α_D^{25} +5.5° ± 0.4 (H$_2$O). *Anal.* Calcd.: 43.3% C, 9.5% H, 10.1% N, 25.6% Cl. Found: 43.5% C, 9.7% H, 10.4% N, 25.6% Cl.

(7) *Anal.* Found: 58.5% C, 12.0% H, 13.8% N.

(8) α_D^{25} −4.7 ± 0.4° (H$_2$O). *Anal.* Found: C, 43.5; H, 9.5; N, 10.2%; Cl, 25.4%.

diethanol[9] were isolated in small amounts as by-products, the quantities increasing when the excess of aminobutanol was decreased. An interesting alternative synthesis, reductive alkylation of 2-aminobutanol with glyoxal using sodium borohydride[10] as reducing agent, gave good yields.

This work has shown that in mice the dextro form of 2,2′-(ethylenediimino)-di-1-butanol is more active and less toxic than streptomycin when administered parenterally and possesses an oral efficacy index (ratio of maximum tolerated dose to median effective dose) at least equivalent to that of isoniazid. A series of papers is in preparation covering studies of numerous homologs and of various analogs and modifications of the functional groups of this chemotherapeutic agent.

(9) *meso*-Dihydrochloride, m.p. 246.5–247.5° dec. (±)-dihydrochloride, m.p. 238–239° dec.

(10) J. H. Billman and A. C. Diesing, *J. Org. Chem.*, **22**, 1068 (1957), used this reagent for reduction of aromatic Schiff bases.

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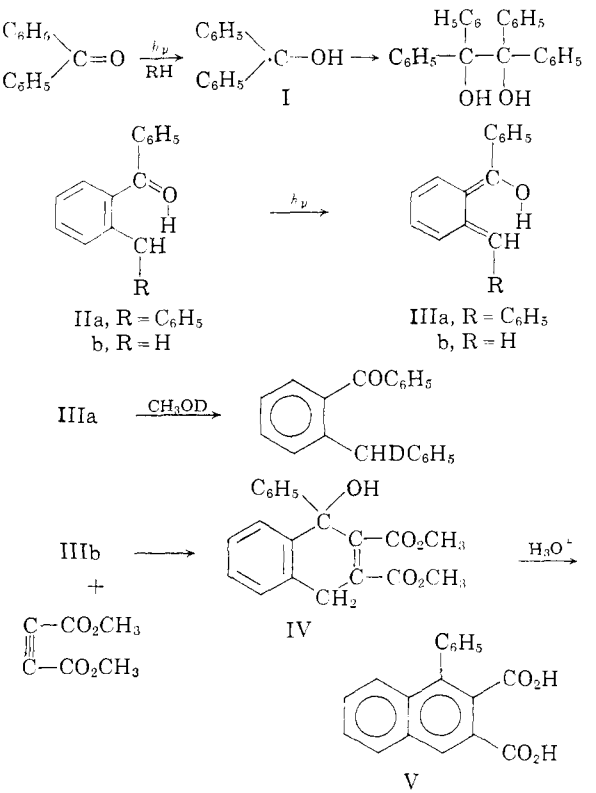
A NEW PHOTOCHEMICAL PRIMARY PROCESS, THE PHOTOCHEMICAL ENOLIZATION OF *o*-SUBSTITUTED BENZOPHENONES

Sir:

We wish to report a new type of photochemical primary process, the photochemical enolization of *o*-substituted benzophenones. Benzophenone readily is reduced photochemically in the presence of hydrogen donors to give benzopinacol *via* a ketyl radical intermediate (I).[1] Photochemical pinacol reduction is suppressed completely and no ketyl radical formation is detected if the benzophenone is substituted at the *ortho* position by an alkyl group containing an α-hydrogen. Instead, *o*-alkylbenzophenone (II) undergoes intramolecular hydrogen transfer to give the corresponding enol under the influence of ultraviolet light. Photochemical enolization of this type has been demonstrated unequivocally by these observations.

o-Benzylbenzophenone (IIa) is extremely stable toward ultraviolet radiation generated by either low pressure or high pressure mercury arcs. The compound was recovered unchanged after prolonged irradiation in alcohol solutions and no pinacol could be detected. When a solution of IIa in CH_3OD was irradiated with a Hanovia S-200 source, the recovered IIa was found to contain 1.04–1.09 atoms of deuterium per molecule,[2] while no deuterium incorporation took place when the same solution was allowed to stand at ordinary laboratory conditions. By n.m.r. spectrometry, all the deuterium atoms were found to be located at the benzylic position.

The photo-enol (IIIb) of *o*-methylbenzophenone (IIb) reacts smoothly with dimethyl acetylenedicarboxylate, a dienophile, to give an adduct (IV) in excellent yield. An equimolar solution of IIb



and dimethyl acetylenedicarboxylate (0.06 mole) in benzene was irradiated with a Hanovia S-200 source at 15–20° for 24 hours. After the solvent was removed, the residue crystallized and no appreciable amount of polymeric material was formed. The residue was recrystallized from benzene–cyclohexane to give IV in 85% yield (m.p. 112°; found: C, 71.25; H, 5.36; λ_{max} 3500 cm.$^{-1}$, 1720 cm.$^{-1}$; strong ultraviolet end absorption). The structure of IV was established by its conversion to 1-phenylnaphthalene-2,3-dicarboxylic acid (V), identical in all respects with an authentic sample.[3] The quantum yield of this photochemical addition is estimated at >0.5. The generality and further applications of this reaction are being investigated.

The authors wish to thank Professor W. A. Noyes, Jr., for some valuable discussion and Mr. Richard Atkinson for his assistance in the preparation of an authentic sample of V. C. R. is indebted to the Petroleum Research Foundation for a graduate fellowship.

(1) C. S. Hammond and W. M. Moore, *J. Am. Chem. Soc.*, **81**, 6334 (1959), and references therein.

(2) Deuterium analysis by Dr. Josef Nemeth of Urbana, Illinois.

(3) A. Michael, *Ber.*, **39**, 1912 (1906).

(4) Alfred P. Sloan Fellow.

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RECEIVED FEBRUARY 27, 1961

THE PHOTOCHEMICAL REARRANGEMENT OF HYPOCHLORITES

Sir:

In a recent communication[1] we adumbrated a photochemically induced rearrangement of hypohalites of the general type (A) → (B) (X = halo-

(1) D. H. R. Barton, J. M. Beaton, L. E. Geller and M. M. Pechet, *J. Am. Chem. Soc.*, **82**, 2640 (1960).