use of the $\Delta^{17,20}$-21-hydroxy group[2] as a precursor for the dihydroxyacetone chain. The latter method has been particularly useful for the synthesis of alkyl homologs of cortisone and hydrocortisone because of its applicability to base-catalyzed alkylations. Both of these methods have intrinsic limitations for some applications, however.

A new type of protecting group has been found and consists of two formaldehyde units bridging C_{17}, C_{20} and C_{21}. It results from acid-catalyzed condensation of a 17α,21-dihydroxy-20-ketopregnane with formaldehyde in the presence of a strong acid. Once formed the bismethylenedioxy function can be removed by fairly vigorous treatment with acids.

For example, 50 g. of cortisone in 2000 ml. of chloroform was stirred with 500 ml. of formalin (37% aqueous formaldehyde) and 500 ml. of concentrated hydrochloric acid for 48 hours to yield 39.5 g. of 17,20;20,21-bismethylenedioxy-4-pregnene-3,11-dione m.p. 242–250°. Similarly hydrocortisone, prednisone, prednisolone, 9α-fluorohydrocortisone (properties listed in Table I) and a number of other steroids have given bismethylenedioxy (BMD) derivatives.

TABLE I

PROPERTIES OF 17,20;20,21-BISMETHYLENEDIOXY STEROIDS

Steroid	Yield, %	M.p., °C.	$[\alpha]_D^{CHCl_3}$	C, H Calcd.	C, H Found
Cortisone BMD	70	258–261	+82	68.63 7.51	68.70 7.38
Hydrocortisone BMD	50	217–222	+26	68.29 7.97	68.01 7.97
Prednisone BMD	60	214–217	+57	68.98 7.05	68.60 7.11
Prednisolone BMD	60	270–274	−20	68.63 7.51	68.37 7.70
9α-Fluorohydrocortisone BMD	70	250–260 or 285–290	+30	65.38 7.39	65.74 6.89

In general, the BMD compounds are highly crystalline, high melting solids which are much less polar than the parent steroid as evidenced by solubility and chromatographic behavior. The molecular rotation change from the dihydroxyacetone to the bismethylenedioxy side chain is in a levorotatory direction (ΔM_D −390 to −490°). Although two stereoisomers at C_{20} are theoretically possible, one isomer has been isolated in all instances. The spiroketal grouping is quite stable to acid. For example, cortisone BMD survives 1.25 N hydrochloric acid in 50% methanol for 18 hours at 30°, or 1 N sulfuric acid in 90% methanol for 11 hours under reflux.

Removal of the bismethylenedioxy function to reform the dihydroxyacetone side chain is best accomplished with aqueous organic acids such as formic or acetic acid. Heating the BMD derivative in 60% formic acid at steam-bath temperature for ten to thirty minutes gives the parent steroid directly in 50–75% yield. Alternatively, 50% acetic acid at 100° for seven hours, followed by acetylation and chromatography, has given the corresponding 21-acetate in 50–60% yields.

These BMD derivatives have been subjected to a variety of reaction conditions without damage to the protected side chain: *e.g.*, alkylations, acylations, dioxolanations, brominations, oxidations, reductions, and acid catalyzed rearrangements. In all cases the spiroketal function remains essentially untouched. Details of these transformations will be the subject of future communications from these laboratories.

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RECEIVED FEBRUARY 13, 1958

DEMONSTRATION OF AN ATOM TRANSFER PROCESS BY ELECTRON SPIN RESONANCE[1]

Sir:

The electron spin resonance spectrum of a dilute solution of the sodium ketyl of benzophenone in 1,2-dimethoxyethane consists of more than eighty hyperfine components in a span of about 28 oersteds. While we have not yet made a complete analysis of the spectrum, we have determined by comparison with the spectra of the corresponding lithium and potassium ketyls that a splitting by the nuclear moment of Na^{23} (spin 3/2) occurs. The magnitude of this splitting is about 1 oersted or about 2.8 megacycles per second. The fact that it occurs indicates that each ketyl molecule retains its sodium atom for a time $\sim 3 \times 10^{-7}$ second or longer.

In the presence of benzophenone an exchange reaction occurs. The over-all reaction is $NaOC(C_6H_5)_2 + OC(C_6H_5)_2 = OC(C_6H_5)_2 + NaOC(C_6H_5)_2$. The question whether the reaction proceeds by transfer of sodium atoms or by separate and uncorrelated transfers of electrons and sodium ions may be answered by the electron spin resonance method. Should each unpaired electron interact with the nuclear magnetic moments of many sodium atoms as well as with the moments of many protons as the exchange reaction proceeds the resonance spectrum would collapse into a single line. On the other hand, if each electron carries its sodium nucleus with it during many exchanges (atom transfer), the spectrum would collapse into four lines, each line corresponding to one of the four possible orientations of the sodium nuclei.

In the presence of benzophenone at ~ 2 M we observe the latter possibility; the original spectrum of more than eighty lines has collapsed into four equally intense lines with separation 1.1 oersteds. Our observations are compatible with a second order rate constant for the exchange $K \geq 5 \times 10^7$ liter mole^{-1} sec.$^{-1}$. At a concentration of benzophenone ~ 2 M the mean life of each ketyl molecule $t_K \leq 10^{-8}$ second while the mean time of

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staying together of electron and sodium $t_{Na} \geq 3 \times 10^{-7}$ second.

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EFFECT OF 1-PHENYL-2-HYDRAZINOPROPANE, A POTENT MONOAMINE OXIDASE (MAO) INHIBITOR, ON BRAIN LEVELS OF NOREPINEPHRINE AND SEROTONIN

Sir:

We have synthesized certain hydrazine analogs,[1] in the hope of obtaining sympathomimetic substances with greater affinity for the cell receptor sites and increased stability toward metabolic degradation. One such compound, α-methylphen-

—$CH_2CH(CH_3)$—NH—NH_2·HCl (JB-516)

ethylhydrazine hydrochloride exhibited amphetamine-like activity. In addition, it was demonstrated by Horita[2] to be an MAO inhibitor, many times more potent than iproniazid.

The therapeutic significance of the MAO inhibitor iproniazid in the treatment of depressed mental conditions[3] prompted us to report on the preparation, preliminary pharmacological and biochemical effects of this new hydrazine derivative. Phenyl-2-propanone was treated with methanolic hydrazine hydrate to form phenyl-2-propanone hydrazone in 80% yield, b.p. 101–103° (0.30 mm); found: N, 18.46; $n^{20}D$ 1.5613. The hydrazone was reduced to α-methylphenethylhydrazine with platinum oxide in ethanol–acetic acid solution, b.p. 82–86° (0.50 mm.); yield 55–60% (found: N, 18.71; $n^{20}D$ 1.5401). The monohydrochloride melted at 122–124° (found: Cl, 18.97; C, 57.95; H, 8.10; N, 15.01.)

Five mg./kg. of JB-516 produced marked central stimulatory effects in rabbits similar to those of amphetamine. Lower doses (1 mg./kg.) exerted no obvious effects. However, this dose appeared to inhibit brain monoamine oxidase activity,[4,5] since rabbits pretreated with 1 mg./kg. of JB-516 and then given 5 mg./kg. reserpine exhibited excitation instead of depression.

Monoamine oxidase has been shown to have a major role in the physiologic inactivation of both serotonin and norepinephrine in brain.[6]

Since these substances may be involved in the regulation of certain brain functions,[7,8] it was of interest to investigate the effect of JB-516 in low dosage on serotonin and norepinephrine levels in brain. JB-516 (1 mg./kg.) and iproniazid (10 mg./kg.) were administered daily (s.c.) to rabbits for five days. The levels of the amines, in brain stem, measured by methods previously described[9,10] rose slowly and reached two to three times the normal value within five days. By the third or fourth day central stimulation was evident. The administration of 5 mg./kg. of iproniazid and 50 mg./kg. of isoniazid daily for 5 days elicited neither excitation nor an increase in the levels of the brain amines. The effects of the various drugs on brain levels of norepinephrine and serotonin are summarized in Table I. Each value represents the average of three animals.

Mg./kg.				
JB-516	Iproniazid		Isoniazid	
1.0	10	5	50	Controls
Norepinephrine levels (γ/g. tissue)				
0.95	1.1	0.43	0.40	0.40
Serotonin levels (γ/g. of tissue)				
1.6	0.92	0.60	0.58	0.58

These results suggest that JB-516 is at least ten times as active as iproniazid in eliciting central excitation and a rise in brain levels of nor-epinephrine and serotonin. The increase in nor-epinephrine may be related to central action of JB-516; in this regard it is noteworthy that large doses of 3,4-dihydroxyphenylalanine, a norepinephrine precursor, cause central excitation which is enhanced by pretreatment with iproniazid.[11]

In summary, the replacement of an amino group by a hydrazino moiety in amphetamine has yielded a compound which embodies the effects of amphetamine but is in addition a very potent MAO inhibitor. The compound is now undergoing extensive clinical investigation for treatment of depressed mental conditions.

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INTERCONVERSION OF VOLATILE BORANES BY BASIC REAGENTS

Sir:

All of the known effective methods of converting one volatile boron hydride to another have been adjustments of physical conditions governing decomposition-type reactions—as in the conversion of diborane mostly to pentaborane-9 by fast-flow methods at elevated temperatures,[1] or mostly to pentaborane-11 by flow at higher pressures and lower temperatures,[2,3] or to tetraborane by a partial reversal of the process.[2] We now report that some borane interconversions can be done efficiently by the action of appropriately chosen chemical reagents, well below room temperature and

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