Synthesis of Oxime Esters and Ethers as Potential Psychotropic Agents

By BILLY B. WYLIE, EUGENE I. ISAACSON, and JAIME N. DELGADO

Esters and ethers of benzophenone oxime and dibenzosuberone oxime were synthesized as potential medicinal agents. The esterifications were effected by treating the oximes with benzoyl, 3,4,5-trimethoxybenzoyl, and diphenylcarbamyl chlorides. The *O*-alkylations of benzophenone oxime and dibenzosuberone oxime were accomplished by the nucleophilic substitution of γ-dimethylaminopropyl, β-dimethylaminoethyl, and benzyl chlorides. In the course of this investigation, 13 compounds were prepared for pharmacological evaluation.

PREVIOUS work in these laboratories has demonstrated that oxime derivatives with the appropriate pharmacophores possess interesting pharmacologic properties, *i.e.*, certain esters and ethers derivable from 1-methyl-4-oximinopiperidine and 3-oximinotropane exhibit anticholinergic activity (1). Thus, inasmuch as oximino ethers and esters modeled after conventional anticholinergics were found to possess anticholinergic activity, the synthesis of oximino ethers and esters bearing a resemblance to amitriptyline was undertaken, for these compounds might likewise possess psychotropic activity.

Two series of compounds were prepared by treating benzophenone oxime and dibenzosuberone oxime with appropriate acid, benzyl, and aminoalkyl halides to yield compounds possessing stereoelectronic features specifically chosen for potential biological activity. Studies of amitriptyline (I) and congeners indicate that a nitrogen atom need not be present, either in the seven-membered cyclic portion, or in the immediate region of the first atomic position of the side chain in order for the compound to possess pronounced physiological effect (2). The compound amitriptyline does not possess the cyclic nitrogen present in imipramine but instead possesses the unsaturation of a carbon to carbon double bond at a comparable position, and yet resembles imipramine in its spectrum of activity. Additionally, for nortriptyline and desipramine, desmethyl congeners of the above compounds, similar statements apply (2). It is possible that high electron density in this region contributes to the desired pharmacodynamic activity. In one case there is the double bond between the cyclic and side chain portion, and in the other, the tertiary nitrogen atom within the seven-membered cyclic system, either of which places high electron density near the same position. Accordingly, the compounds described in this report (II and III) were designed with the oximino group as a center of high electron density at an analogous position.

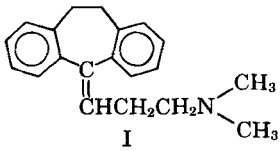
Certain intrinsic stereochemical differences between the compounds prepared and amitriptyline should be expected to influence the efficiency of the drug–receptor interaction. Structural alterations also can be expected to alter the partition coefficient and therefore the distribution patterns of the compounds as well.

In view of these considerations, it became of interest to prepare these oximino esters and ethers. Certain of these compounds possess a basic nitrogen function, whereas others do not; hence, subsequent structure-activity studies might indicate whether such a basic nitrogen function is necessary for central activity. Additionally, benzophenone oxime γ-dimethylaminopropyl ether was synthesized and characterized as the *N*-methyl quaternary salt in order to study its peripheral anticholinergic activity which will be compared with those oxime esters derivable from tropinone (1).

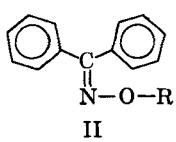
The oximes, starting materials for the synthesis of esters and ethers, were prepared by conventional methods; benzophenone oxime was prepared according to the method of Lachman and Noller (3) and the procedure of Davis *et al.* (4) afforded the dibenzosuberone oxime.

A number of methods (5–8) were studied for the preparation of these oxime esters and ethers, however, the following were found to be more expedient and practical. The synthesis of the oxime esters was accomplished by an esterification procedure in which the acylating agent is an acyl chloride dispersed in anhydrous benzene. The method of Gass and Bope (9) was instituted by the introduction of pyridine, which in Gass and Bope's experience resulted in the formation of pyridinium chloride and the conversion of syn-oximes to nitriles *via* the anti-oximes. Blatt and Barnes (10), however, reported that when pyridine was used in the esterification of benzophenone oxime with an acyl chloride, rearrangements were not detected; these workers also noted that rearrangements occur only in the presence of acid chlorides such as benzenesulfonyl chloride. In accordance with the work of Blatt and Barnes, the esters described herein were prepared in good yields by the pyridine-promoted acylation method.

The oxime ethers were prepared expeditiously by the following route. First, the oxime was converted to the sodium salt by means of the addition of sodium hydride to a solution of the oxime in anhy-



I



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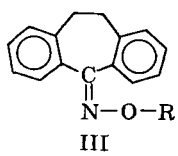

III

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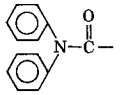
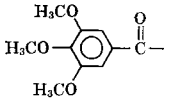
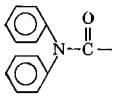
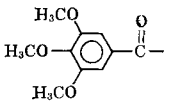
TABLE I.—PHYSICAL CONSTANTS AND ANALYTICAL DATA

R	Compd.	M.p., °C.	% Yield	Empirical Formulas	Anal., % Calcd.	Found
	*1*	98–99	93	$C_{20}H_{15}NO_2$	C, 79.71 H, 5.02	79.63 5.10
	*2*	181–182	89	$C_{26}H_{20}N_2O_2$	C, 79.57 H, 5.14	79.37 5.43
	*3*	128–129	92	$C_{23}H_{21}NO_5$	C, 69.86 H, 5.35	70.18 5.54
	*4*	142.5–143.5	64	$C_{22}H_{17}NO_2$	C, 80.69 H, 5.23	80.39 5.59
	*5*	148–149	73	$C_{28}H_{22}N_2O_2$	C, 80.35 H, 5.29	79.86 5.45
	*6*	119–120	65	$C_{25}H_{23}NO_5$	C, 71.79 H, 5.15	71.78 5.01

drous ethyl alcohol. Subsequently, the aminoalkyl halide or benzyl chloride was dissolved in anhydrous ethyl alcohol and added dropwise to the refluxing solution of the oxime salt; this procedure yielded the expected products whose identities were confirmed by elemental analyses.

EXPERIMENTAL[1]

Synthesis of the Oximes.—*Benzophenone Oxime.*—This compound was prepared from benzophenone (100 Gm., 0.53 mole), hydroxylamine hydrochloride (60 Gm., 0.89 mole), and sodium hydroxide (110 Gm., 2.75 moles) according to the method of Lachman and Noller (3).

Dibenzosuberone Oxime.—The procedure of Davis *et al.* (4) was followed by treating dibenzosuberone (6.0 Gm., 0.03 mole) with hydroxylamine hydrochloride (3.0 Gm., 0.045 mole) in anhydrous redistilled pyridine (100 ml.).

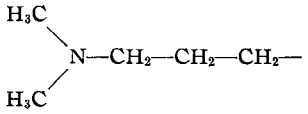
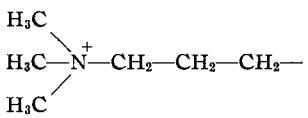
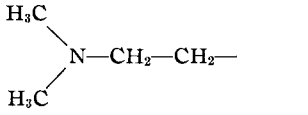
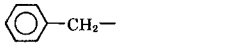
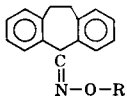
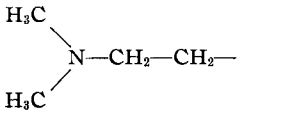
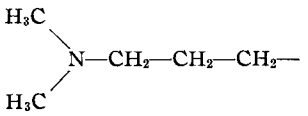
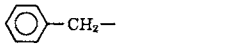
Synthesis of Oxime Esters.—The compounds, together with their respective melting points and analytical data, are listed in Table I. Each was prepared according to the method described under *Benzophenone Oxime Benzoate.* These compounds were purified by recrystallization from isopropyl alcohol.

Benzophenone Oxime Benzoate.—Benzophenone oxime (3.0 Gm., 0.016 mole), benzoyl chloride (2.05 Gm., 0.014 mole), and redistilled anhydrous pyridine (1.15 Gm., 0.016 mole) were added to anhydrous benzene (50 ml.) contained in a 250-ml. flask. The mixture was refluxed for 3 hr., then cooled and extracted with water (three 100-ml. portions). The benzene solution was dried over anhydrous potassium carbonate, and the benzene distilled off under reduced pressure, leaving a crystalline residue which was recrystallized from isopropyl alcohol. The yield was 4.3 Gm. (93% of theory). Repeated recrystallization from isopropyl alcohol gave 2.1 Gm. of analytically pure material, m.p. 98–99°.

Synthesis of Oxime Ethers.—The compounds, together with their respective melting points and analytical data, are listed in Table II. Each was prepared according to the method described for benzophenone γ-dimethylaminopropyl ether. The solvent of recrystallization for the picrate derivatives was ethyl alcohol, with one exception: isopropyl alcohol was the solvent utilized for the recrystallization of dibenzosuberone oxime β-dimethylaminoethyl ether. The methyl iodide derivative of benzophenone oxime γ-dimethylaminopropyl ether was recrystallized from chloroform.

[1] Reported melting points are uncorrected. A Thomas-Hoover Unimelt apparatus was used for melting point determinations. Dr. K. W. Zimmerman, University of Melbourne, Melbourne, Australia, and Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., conducted the elemental analyses.

TABLE II.—PHYSICAL CONSTANTS AND ANALYTICAL DATA

R	Compd.	M.p., °C.	% Yield	Empirical Formulas	Anal., % Calcd.	Found
						
	*7*[a]	123–124	75	$C_{24}H_{25}N_5O_8$	C, 56.13 H, 4.93	56.11 4.83
	*8*[b]	190.5–191.5		$C_{19}H_{25}N_2OI$	C, 53.38 H, 5.89	53.50 6.21
	*9*[a]	103.5–104	81	$C_{23}H_{23}N_5O_8$	C, 55.71 H, 4.67	55.69 4.97
	*10*	58–59	87	$C_{20}H_{17}NO$	C, 83.59 H, 5.92	83.79 6.15
						
	*11*[a]	137–138	89	$C_{25}H_{25}N_5O_8$	C, 57.39 H, 4.82	57.20 5.07
	*12*[a]	168–168.5	71	$C_{26}H_{27}N_5O_8$	C, 58.09 H, 5.06	57.50 5.00
	*13*	107–108	75	$C_{22}H_{19}NO$	C, 84.30 H, 6.11	84.07 6.21

[a] Characterized as the picrate. [b] Characterized as the methyl iodide.

Benzophenone Oxime γ-Dimethylaminopropyl Ether.—Benzophenone oxime (9.85 Gm., 0.05 mole) was dissolved in absolute ethyl alcohol (200 ml.) with the aid of heat and the mixture then cooled in an ice bath. To this solution was added, with stirring and cooling, sodium hydride (4.8 Gm. of a 51.6% mineral oil dispersion, 0.085 mole). γ-Dimethylaminopropyl chloride hydrochloride (8.4 Gm., 0.057 mole) dissolved in the minimum amount of hot absolute ethyl alcohol then was added dropwise with stirring to the refluxing reaction mixture. The mixture was refluxed and stirred for 4 hr. The hot ethanolic solution then was filtered and the ethyl alcohol distilled off under reduced pressure. Diisopropyl ether was added, the mixture again filtered, and the diisopropyl ether removed from the filtrate by distillation under reduced pressure leaving a residue. The yield was 9.5 Gm. (75% of theory).

The compound was characterized as the picrate and methyl iodide derivatives. The melting point of the picrate after repeated recrystallization from ethyl alcohol was 123–124°.

SUMMARY

The synthesis of two series of oxime esters and ethers is reported. The members of one series were prepared from benzophenone oxime, while the compounds of the other series are derivatives of dibenzosuberone oxime. The esterifications were effected by pyridine-promoted acylation with acid chlorides. The *O*-alkylation of the oximes was accomplished by treating the oxime with an equimolar quantity of sodium hydride in ethanol followed by the appropriate alkyl chloride.

In view of the premise that led to the synthesis of these compounds, the pharmacologic evaluation which is presently in progress should lead to interesting structure-activity relationships. The results of the structure-activity studies will be reported at a later date.

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Isolation of a Potential Antitumor Fraction from *Rumex hymenosepalus*

By JACK R. COLE and LEONARD BUCHALTER

Extracts of *Rumex hymenosepalus* have shown antitumor activity against the Sarcoma 180 and Walker 256 test systems of the Cancer Chemotherapy National Service Center, Bethesda, Md. The extracts have been fractionated by means of solvent extraction and paper chromatography into two distinct fractions. The partial characterization of these fractions is described, including the characterization of leucocyanidin as one of the constituents and the identification of benzoic acid as a hydrolysis product of a polyphenolic ester.

RUMEX HYMENOSEPALUS, a dicotyledon of the family *Polygonaceae*, also known by the common name canaigre, is a plant native to the southwestern United States. In tests performed on the various extracts of the plant by the Cancer Chemotherapy National Service Center, it was discovered that the tannin-containing fraction of the plant exhibited antitumor activity. An investigation of this fraction was begun in order to attempt to identify the precise chemical character of the antitumor substance. It should be noted at this point that the response was irregular. Some fractions would show activity in a series of tests; however, upon repetition, the activity would be lost.

A literature search revealed the existence of several methods of extracting tannins from the plant as employed by leather chemists. Chemical compounds already discovered in the plant include substances such as chrysophanic acid, physcion (1), and possibly emodin (2). Polyphenols are said to predominate in canaigre tannins (3). Members of this classification of compounds vary little in phenolic reactivity and therefore are very difficult to separate chemically (3). Polyphenols are capable of a great deal of mutual solubilization, resulting in solid solutions which tend to behave as if they were single substances (4). The roots, the major tannin-containing part of the plant, also contain sugars and starches, which make the usual methods of tannin removal more complicated (4). Therefore, a special method of tannin extraction was developed to fill the requirements of this investigation.

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EXPERIMENTAL

Extraction.—Six hundred grams of the frozen tuber-like roots of the plant were ground into a damp reddish-brown meal-like material in a Wiley mill equipped with a 4-mm. size screen. The ground material was then washed with petroleum ether and ethyl ether. The residues obtained from these extractions were set aside for possible future investigation.

The plant marc was air dried for a 24-hr. period. It was then extracted with 4 L. of a 95% ethanol–methanol (1:1) mixture for 120 hr. The resulting reddish-brown solution was separated from the marc by filtration and allowed to evaporate to dryness. The plant marc was discarded.

The amorphous brown residue of the methanol–ethanol extraction was dissolved in approximately 1 L. of distilled water. The solution was then washed repeatedly with a total of 2 L. of chloroform.

The washed water extract was then frozen and lyophilized at −50° to dryness. Approximately 120 Gm. of a light orange-brown semicrystalline powder was obtained. The lyophilized extract was submitted to the Cancer Chemotherapy National Service Center for antitumor testing. Testing in Walker 256 test system (5) gave a value of 35% t/c (test/control) at 60 mg./Kg. Also against the Sarcoma 180 test system (5) a value of 14% t/c at a dose of 90 mg./Kg. was obtained. These results indicate definite activity.

Physical and Chemical Characteristics.—The amorphous orange-brown powder obtained was subjected to a series of tests to determine functional composition. Elementary analysis by sodium fusion showed the absence of nitrogen, sulfur, or halogens. Solubility tests indicated the presence of weakly acidic materials. Aqueous solutions of the extract demonstrated indicator-like properties by color changes with change of pH. Ferric chloride, 5% aqueous solution, gave a blue-black color reaction,