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Anti-Narcoleptic Agent Modafinil and Its Sulfone: A Novel Facile Synthesis and Potential Anti-Epileptic Activity

Nithiananda Chatterjie,[1,4] James P. Stables,[2] Hsin Wang,[3] and George J. Alexander[1]

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We report a facile procedure to synthesize racemic modafinil (diphenylmethylsulfinylacetamide), which is now being used in pharmacotherapy, and its achiral oxidized derivative (diphenylmethylsulfonyl acetamide). Modafinil is of interest more than for its potential anti-narcoleptic activity. It has also been reported to have neuroprotective properties and may potentially be effective in the enhancement of vigilance and cognitive performance. Finally, it may also protect from subclinical seizures that have been implicated as causative factors in autistic spectrum disorders and other neurodegenerative conditions. This agent can now be synthesized simply and in larger amounts than previously, making it more readily available for testing in various research modalities. The described procedure also lends itself to production of several other amides of potential interest. We are currently in the process of synthesizing and testing several new derivatives in this series. The anticonvulsant properties of modafinil and its sulfone derivative have not previously been extensively described in the literature. It may be of interest to note that the oxidized derivative of modafinil is also nontoxic and almost as effective as an anticonvulsant as the parent.

KEY WORDS: Anti-epileptic; anti-narcoleptic; chemical synthesis; chirality; modafinil; modafinil sulfone; neuroprotectant; toxicity.

INTRODUCTION

Our interest in synthesis of modified neuroactive compounds (1) has led us to consider modafinil (**1**), a stimulant and anti-narcoleptic agent that is finding increasing use in a number of neurological areas. The compound was originally prepared by a rather tedious route described in a patented procedure (2). More recently, its preparation has been reported by Mu Baochun et al. (3). We believe that this compound has many interesting properties and possible alternative uses in addition to its recognized anti-narcoleptic actions (4–8). Not having been able to obtain it from the patent holder, we proceeded to explore alternate synthetic pathways and settled on a convenient synthesis, which permitted us to produce this compound along with a primary derivative, the sulfone (**2**) in sufficient quantities for whole-animal studies. The current, more facile method starts with benzhydryl bromide and sodium thiolacetate in aqueous acetone, which reacts directly to form diphenylmethylthioacetic acid (**3**), possibly by an ionic mechanism. This resultant compound can be converted to its acid chloride that, in turn, may be used to acylate ammonia. The ensuing primary amide (**4**) may be gently oxidized by H_2O_2 to form the corresponding sulfoxide (modafinil, **1**) and, under more vigorous conditions, the

[1] New York State Institute for Basic Research in Developmental Disabilities, Staten Island, New York 10314, USA.
[2] Preclinical Screening Program, NINDS, Bethesda, Maryland 20892, USA.
[3] College of Staten Island, CUNY, Staten Island, New York 10314, USA.
[4] Address reprint requests to: Nithiananda Chatterjie, Ph.D., Department of Neurochemistry, New York State Institute for Basic Research in Developmental Disabilities, 1050 Forest Hill Road, Staten Island, NY 10314, USA. Tel: (718) 494-5247; Fax: (718) 698-7916; E-mail: chemexp@aol.com

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Table I. Protection from Maximal Electroshock (MES) Seizures After i.p. Injection or Oral Intake of Modafinil (**1**), Modafinil Sulfone (**2**), or Intermediate Acid (**3**)

		Protection			
		i.p.		Oral	
Compound	Dose	30 min	4 h	30 min	4 h
Rats					
modafinil (**1**)	30 mg/kg	50%	—	25%	25%
modanfil (**1**)	60–75 mg/kg	—	—	25%	25%*
sulfone (**2**)	30 mg/kg	50%†	25%	—	—
acid (**3**)	30 mg/kg	25%‡	—	75%	—
Mice					
modafinil (**1**)	300 mg/kg	100%	—	25%	25%
sulfone (**2**)	300 mg/kg	50%	—	—	—
acid (**3**)	300 mg/kg	0§	—	—	—

Note: Mice were also tested with the chemoconvulsant metrazol after 300 mg/kg modafinil, and 60% were protected from seizures.
* The response to MES in 4–8 rats at 1/4, 1/2, 1, 2, 4 and 6 hrs after oral intake of 60–75 mg of modafinil (n=36); at all time-points 1/4 or 2/8 subjects were protected from seizures.
† The response in 1 hr after injection was also 50%.
‡ The response was also 25% at 1/4 hr, 1 hr and 4 hrs.
§ The compound was toxic; animals were limp and unresponsive.

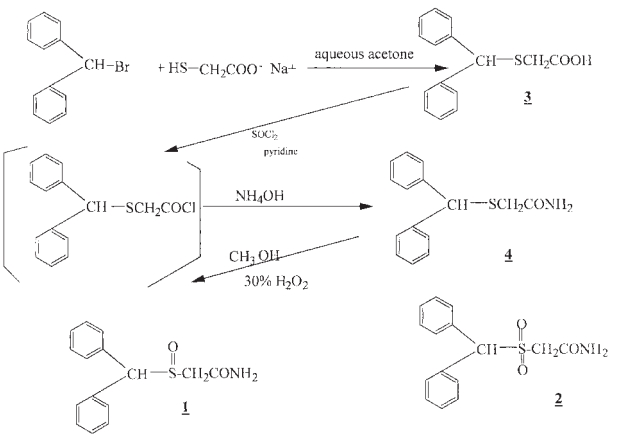
modafinil sulfone (**2**), whose anticonvulsant and biological properties have not been described extensively in the literature. Additionally, this procedure is also uniquely suitable for large-scale preparation of modafinil and its congeners.

EXPERIMENTAL PROCEDURE

The new compounds were prepared according to modified procedures published in the patent literature. Starting materials and solvents were obtained commercially from Fluka and/or Aldrich Chemical Corp. (St. Louis, MO, USA). Thin layer chromatography (TLC) was performed on silica gel plates supplied by Analtech, Inc. (Newark, DE, USA). Solvent system was EtOAc:MeOH:NH_4OH, 100:10:3 by volume. Melting points are uncorrected. Mass spectra were obtained by positive electrospray technology after dissolving samples in acetonitrile solvent. Nuclear magnetic spectra (NMR) were obtained on a Varian Unity 200 MHz or Unity Inova 600 MHz spectrophotometers in solvent, $CDCl_3$, or as indicated. Elemental analyses were obtained from Huffmann Laboratories Inc. (Golden, CO, USA) and are within 0.4% of the theoretical. Infrared (IR) spectra were obtained on a Nicolet Magna-IR 550 spectrometer. Samples were dissolved in $CHCl_3$ and applied on a 3M-IR card as a dry film. A baseline correction was applied using $CHCl_3$ as a blank. Mass spectrometric analyses were performed by positive electrospray on an Agilent Technologies 1100LC/MSD machine at Hunter College Mass Spectrometry Facility (New York, NY, USA). Tests of biological activity, including toxicological evaluation and a study of anti-epileptic potential, were performed by the Anti-Epilepsy Drug Screening Program (ASP) at the Preclinical Screening Program of the National Institute of Neurological Disorders and Stroke, National Institutes of Health (Bethesda, MD, USA).

RESULTS

The chemical pathway leading to modafinil may be represented in Scheme 1.



Scheme 1.

Diphenylmethylthioacetic Acid (3)

Benzhydryl bromide (14.78 gm, 0.059 mole) was dissolved in 75 ml of acetone in a 250-ml round-bottomed flask. To this solution was added dropwise sodium mercaptoacetate (6.59 g, 0.058 mole) in about 60 ml of H_2O; the mixture was stirred under N_2 for 2 h at room temperature and was thereafter warmed at about 60–70°C for 1 h. The reaction mixture was evaporated to dryness and taken up in CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic extract was rejected, and the aqueous phase was treated with acid to pH ~2 and chilled. Suction filtration gave the 6.9 g of the acid (**3**, 46%), mp 125°C. R_f = 0.2. Recrystallization from MeOH/H_2O gave mp 126–128°C. IR (cm^{-1}) was 1703 (strong), 1466, and 1293. ^{1}H-NMR spectrum ($CDCl_3$): δ 7.33–7.10 (m, 10H), 5.29 (s, 1H), and 2.95 (s, 2H). Mass spectrum: (positive electrospray) M/z 276 ($M^+ + NH_4^+$); (negative electrospray) 257 (M^+-1). Elemental analysis, calculated for $C_{15}H_{14}O_2S$: %C = 69.73; %H = 5.46; %S = 12.41. Found: C = 69.73; H = 5.46; S = 12.48.

Diphenylmethylthioacetamide (4)

Diphenylmethylthioacetic acid (19.5 g, 0.076 mole) in 114 ml of dry benzene was taken in a 250-ml round-bottomed flask attached to a reflux condenser, under N_2 gas. To this was added thionyl chloride (~19.5 ml, 0.097 mole) with a dropping funnel. The mixture was stirred at

room temperature with a magnetic stirrer and refluxed for 1 h. Thereafter, the mixture was evaporated under low pressure to give a yellow oil that was taken up in about 100 ml of CH_2Cl_2 and filtered to yield a clear orange solution. This was chilled in ice water and added slowly to an ice-cold solution of concentrated NH_4OH in H_2O (40:40 ml). The ensuing mixture was stirred for 1 h and shaken well in a separatory funnel. The organic layer was dried (Na_2SO_4) and evaporated to dryness to give 14.39 g (54%) of the amide (**4**), mp 108–109°C (lit[2] 110°C). R_f = 0.8. Recrystallization from CH_3OH/H_2O gave mp 109–110°C. IR (cm^{-1}) was 3371, 3188, 1630 (strong), 1466 (strong), 1356, 1229, and 1074. ^{1}H-NMR ($CDCl_3$): δ 7.42–7.29 (m, 10H), 6.52 (broad s, 1H), 5.81 (broad s, 1H), 5.17 (s, 1H), 3.08 (s, 2H). Mass spectrum: m/z 275 ($M^+ + NH_4^+$), 537 ($2M^+ + Na^+$). Elemental analysis, calculated for $C_{15}H_{15}NOS$: %C = 70.03; %H = 5.84; %N = 5.55; %S = 12.45. Found: C = 70.05; H = 5.69; N = 5.50; S = 12.50.

Diphenylmethylsulfinylacetamide (modafinil, 1)

Diphenylthioacetamide (3.46 g, 0.013 mole) was taken in glacial acetic acid (14 ml) with stirring; to this was added ~1.34 ml of 30% H_2O_2 with chilling in ice water. The mixture was left in the refrigerator for 4 h and thereafter worked up by treating it with 70 ml of ice-cold water. The precipitated material was filtered under suction and washed with ice-cold water to give 1.5 g of white crystals (43%), mp 159–160°C. R_f = 0.6. Recrystallization from hot MeOH gave mp 161–162°C (lit[2] mp 164–166°C). IR (cm^{-1}) was 3400 (broad), 1675, 1448 (strong), 1074, and 700 (strong). ^{1}H-NMR spectrum ($CDCl_3$): δ 7.55–7.28 (m, 10H), 7.09 (s, broad, 1H), 5.67 (s, broad, 1H), 5.22 (s, 1H), 3.55 and 3.48 (d, 1H, J = 14.3 Hz), 3.17 and 3.09 (d, 1H, J = 14.3 Hz). Mass spectrum: m/z 274 ($M^+ + 1$); 296 ($M^+ + Na^+$); 547 ($2M^+ + 1$); 569 ($2M^+ + Na^+$); 167 (100% diphenylmethyl cation). Elemental analysis, calculated for $C_{15}H_{15}NO_2S$: %C = 65.93; %H = 5.49; %N = 5.12; %S = 11.72. Found: C = 65.76; H = 5.42; N = 5.22; S = 11.81.

Diphenylmethylsufonylacetamide (2)

Diphenylmethylthioacetamide (2.5 g, 0.009 mole) (reg. No. 118779-53-6) was dissolved in about 12 ml of glacial acetic acid and 3 ml of 30% H_2O_2 and set aside overnight (16 h or more). The next day, the mixture was diluted with 100 ml of H_2O and set aside to cool in the refrigerator. Upon filtration and drying, 2.1 g (80%) of **2** was obtained as a white powder. R_f = 0.89. The melting point of sample after recrystallization from absolute EtOH was 195–197°C. (lit[2] mp 194°C). IR (cm^{-1}) was 3398, 3197, 1666, 1311, and 1129. ^{1}H-NMR (DMSO-d_6): δ 7.71–7.38 (m, 10H and buried amide protons), 6.08 (s, H), 3.74 (s, 2H). D_2O exchange spectrum: 7.63–7.37 (m 10H and partially buried amide protons), 6.03 (s, 1H), 3.78 (s, 2H). Mass spectrum: m/z 307 ($M^+ + NH_4^+$), 601 ($2M^+ + Na^+$). Elemental analysis, calculated for $C_{15}H_{15}NO_3S$: %C = 62.33; %H = 5.22; %N = 4.84; %S = 11.08. Found: C = 62.53; H = 5.42; N = 4.76; S = 11.30.

One aspect of our preparation of modafinil needs further mention. When diphenylmethylthioacetamide (**4**) is being oxidized by H_2O_2, care must be taken to keep the reaction mixture cool, and workup should be done in a timely manner. Allowing the reaction to go to 24 h or longer at room temperature results in the formation of the sulfone (**2**). The paper by Mu et al. (3) does not discuss this possibility. In our hands, the procedure stated therein led to the higher melting sulfone and not the modafinil. Our NMR data for the newly prepared modafinil preparation are in consonance with the data of the patented commercial product. It should be noted that the methylene protons in modafinil are geminally coupled and appear as a pair of doublets. This is due to the fact that the adjacent sulfoxide moiety is chiral, and therefore the methylene protons adjacent to it wind up being diastereotopic with different chemical shifts and coupling. In the sulfone **2**, the methylene protons appear as a singlet due to the fact that the adjacent sulfone moiety is achiral, thus making the two protons equivalent. Modafinil **1** is, however, an equal mixture of enantiomers, as in the reported patent and publication (2,3).

Toxicity

Toxicity was studied in albino male CF #1 mice (20–25 g) and in the male Sprague-Dawley rat (130–140 grams) at the Anticonvulsant Screening Program's preclinical pharmacology laboratories per their standard qualitative evaluations procedures (9). The rotorod technique was employed for assessment of motor impairment in mice. In this test, the inability of an animal to remain on a rotating rod for at least 1 min on 3 successive attempts was viewed as impairment (9,10). Uncompromised animals can easily maintain their balance in the test model. The positional sense and gait test were used to evaluate toxicity in rats (9,10). The relative clinical safety of modafinil (**1**) has previously been established clinically, and the current rodent work, using our newly synthesized material, confirms modafinil's lack of severe side effects. Doses of 30, 100, and 300 mg/kg

were administered to mice with subsequent testing against the maximal electroshock (MES), metrazole, and toxicity models. Testing was performed at $\frac{1}{2}$- and 4-h postadministration of drug at each of the doses. One additional time point was used (6 h) to determine if there might be any active metabolites contributing to observed protection at the other time points. Interestingly, although no toxicity was observed via the i.p. route at either the 1/2-or 4-h time points up to 300 mg/kg, 1 animal was toxic at a lower dose (100 mg/kg) at 6 h postadministration. Additional testing is underway to determine whether this may have been a spurious result.

There was no evidence of toxicity in rats at either 30 or 100 mg/kg (p.o.) or at 30 mg/kg i.p. over 5 time points ranging from 1/4 h to 4 h. In preliminary toxicity tests, the sulfone (**2**) behaved similarly. Here again, mouse testing was taken up to 300 mg/kg, whereas oral testing in rats went as high as 120 mg/kg. The diphenylmethylthioacetic acid intermediate (**3**) was more toxic than the other compounds. Toxicity was observed at doses of 100 and 300 mg/kg at both 1/4 and 4 h. At the dose of 300 mg/kg, all of the animals appeared limp and showed signs of toxicity. The compound did show limited protection in rats at 30 mg/kg by both the oral and i.p. route. Better protection (75%) was seen with oral administration of 100 mg/kg at the 4-h time point. At concurrent times and doses, no toxicity was observed in rats via this route.

Potential Anticonvulsive Effects

To the best of our knowledge, anticonvulsive activity of modafinil has not been thoroughly explored heretofore. In our exploratory experiments, modafinil (**1**) produced a modest protection against both MES and the chemoconvulsant pentylenetetrazol (metrazol).

Testing performed in rats using an oral dose of 30 mg/kg resulted in 25% of the animals being protected from MES-induced seizures at both 1/4 and 4 h. Slightly better protection was observed at the same dose via the i.p. route. Subsequent testing performed with doses administered i.p. up to 75 mg/kg yielded nonlinear results. The same level of protection was observed from doses ranging from 30 to 75 mg/kg. This could be indicative of problems with absorbtion, distribution, or site-saturation. More experimentation is needed to resolve these issues. This data reflects some level of activity in several epilepsy models. The information merits further exploration.

The sulfone of modafinil (**2**) also demonstrated anticonvulsant activity. In rats, the protection against maximal electroshock peaked at 50% using a dose of 30 mg/kg, 1-h postadministration and remained 25% protective at 4 h. Once again, higher dose did not produce the expected increase in protection in a linear manner. At 120 mg/kg, the maximum protection was 25% achieved at 1/2-, 1-, and 4-h postadministration of test compound. Experiments are underway to look at both the i.v. and i.p. routes of administration to determine if this effect is due to absorption. Mouse experiments indicated some MES protection at 4 h using 300 mg/kg. No toxicity was observed at doses up to and including 300 mg/kg at either 1/4 or 4 h.

The intermediate acid (**3**), which was toxic in mice at 100 mg/kg, showed no anticonvulsant activity in mice at 30 or 100 mg/kg. It was active in both the MES and scMET screen at 300 mg/kg but was toxic at 100 mg/kg. This effect may have been due to the toxicity at this level, as the animals were limp and unresponsive. Protection in rats against MES-induced seizure activity was observed at both 30 (25%) and 100 mg/kg (75%) via the oral route. No toxicity at these doses was observed.

DISCUSSION

Several derivatives of small bioactive molecules such as modafinil, amantadine, hydantoins, narcotic antagonists, imidazoles, salicylates, and melatonin are described in the patent literature, but the therapeutic potential of some of them has been obscured for want of further development in terms of testing for anticonvulsant activity and a variety of possible neuroprotective (11,12) and cognition-enhancing effects (13,14). For example, a recent paper describes the possibility that the NMDA antagonist amantadine hydrochloride can serve as a safe and effective treatment for behavioral disturbances, such as hyperactivity and irritability in children with autism (15). We are investigating the possibility of combining amantadine and modafinil with the objective of creating a better bioactive agent. Modafinil, by itself, also finds a possible place in psychiatric treatment (8). Some of these compounds, specifically, modafinil and its oxidized derivative (sulfone), may find use in treatment of preclinical subconvulsive manifestations, thus preventing deterioration due to continued subclinical neuronal hyperactivity (16). As such, these agents, might prove helpful in dealing with autistic and other pervasive developmental disabilities.

The aim of the synthetic work in our laboratory is to extend our studies of new, modified active pharmacophores that are likely to show improved or modified biological activity not only as possible anticonvulsants but as potential therapeutic agents in an array of neu-

rological disorders and as cognition/behavior modifiers. These agents, when developed, may be less toxic and longer acting (17,18) and are likely to benefit the mentally disabled and autistic subjects who frequently suffer from epileptiform episodes and brain discharges that might predispose them to neuronal developmental conditions such as the autistic spectrum disorders. They may also prove of benefit in senile dementias and neurodegenerative conditions, such as Alzheimer's syndrome, cerebral palsy, Parkinsonism, and so forth (12,19,20). We believe that facile chemical syntheses and assays of key agents, such as modafinil and its sulfone, its precursors and derivatives (21), are crucial in that they make available to more researchers important pharmacophoric agents dedicated to the search for new molecular weapons to combat human disease.

In order to produce novel therapies that prevent specific conditions such as epileptiform episodes, concurrent work must also be done to develop new model systems. For example, in the developing organism there is a need for models that respond to compounds that enhance cognition and at the same time prevent neurodegeneration (22). The availability of experimental agents to screen in these systems will be advanced by the development of synthetic methods such as those that enable the facile preparation of modafinil and its congeners. The sharing of these technological processes will greatly expedite the discovery of the new therapies, but financial support for these efforts is crucial if there is to be real progress.

CONCLUSION

In this paper, we report a new and facile procedure to synthesize racemic modafinil, an agent currently being used in human pharmacotherapy. Because the compound is of interest for more than just antinarcoleptic activity, this work not only provides the means to synthesize larger amounts of material more efficiently, but affords access to additional researchers to embark on exploration of the many novel potential pharmacological uses of modafinil and its analogs. The new procedure also provides a cost-efficient means of producing several other amides of potential interest, thus increasing the research community's availability of molecular tools. We are currently in the process of synthesizing and testing various new derivatives in this series. It may be of interest to note that the oxidized form of modafinil is also nontoxic and almost as effective an anticonvulsant as the parent, modafinil. We hope that this effort provides a scientific incentive to other researchers to further the exploration of this and other groups of molecules to combat disease.

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