K. Pierson for pharmacological results.

References and Notes

(1) The benzomorphan nomenclature has received such widespread usage that we have used it in our discussion; however, the numbering shown for compound I and the nomenclature in the Experimental Section follow Chemical Abstracts recommendations.
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Synthesis and Analgesic Activity of Some Long-Acting Piperidinospiro Derivatives of Methadone

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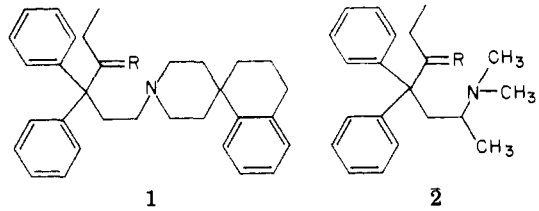
A congener of methadone, in which the metabolically labile C-6 dimethylamino moiety was replaced with a piperidinospiro derivative, was reduced and acetylated. This conversion produced a marked increase in the duration of analgesia, a trend similar to that found for methadone.

Methadone, 4,4-diphenyl-6-(dimethylamino)-3-heptanone (**2a**), is an analgesic currently being used in the maintenance treatment for heroin addiction.

It is known that reduction of the keto moiety of methadone and subsequent acetylation to acetylmethadol results in an increase in the duration of action for analgesia.[1] This transformation also results in an increase in potency.[2]

Compound **1a** is a highly potent, long-acting narcotic analgesic[3] that bears a resemblance to the basic methadone molecule in that this compound is a 4,4-diphenyl-6-amino-3-hexanone derivative. However, the C-6 dimethylamino moiety of methadone, which is the most metabolically labile site,[4] has been replaced by a piperidinospiro derivative. In light of the enhancement in potency and duration of action found for methadone following reduction and acetylation to acetylmethadol, it was of interest to see whether the conversion of the structurally related ketone **1a** to the ester **1c** would produce a similar increase in duration of action. We report herein the results of this conversion.

Chemistry. *N*-(3,3-Diphenyl-4-oxohex-1-yl)-7,8-benzo-3-azaspiro[5.5]undecane (R-4066, **1a**), as the oxalate



1 2

1a, **2a**, R = O
1b, **2b**, R = OH, H
1c, **2b**, R = OAc, H

salt, was reduced with sodium borohydride in 2-propanol to give the crystalline racemic alcohol **1b**. The alcohol **1b** was converted to the acetate **1c** by treatment with acetic anhydride in pyridine. The oily free amine was converted to its sulfate salt by treating with methanol–sulfuric acid and extracting with methylene chloride. This yielded a light beige crystalline solid. All compounds were characterized by NMR, IR, MS, and elemental analysis, and their physical and chemical properties are summarized in Table I.

Pharmacology. The test compounds were administered to Sprague–Dawley rats by oral intubation, and the analgesic activity was evaluated by determining each compound's ability to inhibit the warm-water tail withdrawal reflex.[5] For each test compound, activity was evaluated at three dose levels. Ten animals were used at each dose. ED_{50} values were determined by probit analysis.[6] Animals were considered analgesic if the tail withdrawal latency was greater than 4 s. Animals were tested every hour until 24 h after drug. The onset, peak, and duration of action were measured from duration-response plots for the highest dose administered for each compound. Mean and standard errors of the mean latency values at each test time were determined using only those animals with tail withdrawal times greater than 4 s. Potency ratios (relative to methadone) were determined according to the method of Litchfield–Wilcoxon.[6] Statistical analysis of the slopes of the dose–response plots showed them to be parallel within experimental error.

The ED_{50} values for these compounds, determined by the results of the warm-water tail withdrawal test and shown in Table II, are 0.07 mg/kg for compound **1a** and 0.14 mg/kg for compounds **1b** and **1c**. The ED_{50} value for methadone is in general agreement with the value reported by Smits and Myers (10 mg/kg).[7]

A comparison of the potency ratios (Table II), computed relative to methadone, shows that the racemic mixtures of compounds **1b** and **1c** are half as potent (ratio = 106) as compound **1a** (ratio = 212) which possesses to chiral center. This may indicate the existence of only one active stereoisomer as has been shown in the methadone–me-

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Table I. *N*-(3,3-Diphenyl-4-oxohex-1-yl)-7,8-benzo-3-azaspiro[5,5]undecane and Derivatives

Compd	Mp, °C	Recrystn solvent[a]	Formula	Analyses[b]	Mass spectra (M^+)	Yield, %
1a	205-206		$C_{32}H_{37}ON$	C, H, N	451	
1b	73-75	A	$C_{32}H_{39}ON$	C, H, N	395 (M − 58)[c]	98.5
1c	134-135	B	$C_{68}H_{84}O_8N_2S$	C, H, N	495	73

[a] A = ether; B = CH_2Cl_2-pentane. [b] Analytical results were within 0.4% of the theoretical values. [c] M − 58 indicates loss of CH_3CH_2CHO.

Table II. Activity of Compounds 1a-c Determined by the Warm-Water Tail Withdrawal Test

Compd	ED_{50}, mg/kg po[a,b]	Onset, h[c]	Time to peak effect, h[c]	Duration of action, h	Potency ratio
Methadone (2a)	14.8	0.5	4.0	8.0	1
1a	0.07 (0.03-0.19)	1.0	2.0	3.0	212
1b	0.14 (0.09-0.21)	0.5	4.0	6.5	106
1c	0.14 (0.11-0.18)	0.5	6.0	20.5	106

[a] ED_{50} values are expressed in terms of milligrams of free base per kilogram. Numbers in parentheses indicate 95% confidence limits. [b] Rats are considered analgesic if the warm-water tail withdrawal reflex time is ≥4 s. [c] Numbers are average values for all animals exhibiting analgesia.

thadol–acetylmethadol series.[8] The relative potencies were **1a > 1b = 1c**.

The duration of action, shown in Figure 1 of the acetyl derivative **1c**, was longer (20.5 h) than that of the alcohol **1b** (6.5 h) which, in turn, is longer than that of the parent ketone **1a** (3.0 h). The relative durations of action were **1c > 1b > 1a** (20.5, 6.5, and 3.0 h, respectively). For each compound the time to reach peak effect increased with the increase in the duration of action. The relative times to peak effect were **1a < 1b < 1c** (2, 4, and 6 h, respectively). The relative times of onset were **1a > 1b = 1c** (1.0, 0.5, and 0.5 h, respectively).

Biological testing of these compounds indicates a trend similar to that observed for methadone. Reduction and acetylation produces a marked increase in the duration of action. However, the relative potencies are not similar to those found for the methadone series. Conversion of the alcohol of the methadone series to the ester causes a large increase in the potency, whereas in our series there was no change. Reduction of the keto moiety to the alcohol caused a decrease in the potency of the methadone series. Similarly, in our series there was a decrease in potency.

Experimental Section

Chemistry. Preparation of 1b. To 100 mg of **1a** dissolved in 10 mL of 2-propanol was added 100 mg of sodium borohydride with stirring. After 24 h the 2-propanol was removed under vacuum, 10 mL of ether added, and the mixture extracted with brine and dried over sodium sulfate. The ether was removed by rotary evaporation, giving 99 mg (98.5%) of oily **1b**. The oil was dissolved in ether and, upon standing for 2 days, white crystals separated: mp 73–75 °C; NMR (CCl_4) δ 4.0 (m, 1 H); IR (KBr) 3400, 1120 cm^{-1}; MS *m/e* 395 (M^+ − 58) which indicates loss of CH_3CH_2CHO.

Preparation of 1c. To 100 mg of **1b** were added 2 mL of pyridine and 1 mL of acetic anhydride in a 25-mL single-neck round-bottom flask. The mixture was stirred at room temperature overnight under an atmosphere of nitrogen. To the mixture was added 1 mL of H_2O and the stirring continued for 0.5 h. The mixture was added to 25 mL of dichloromethane in a separatory funnel, extracted with 1 N HCl (3 × 25 mL), 3 N NaOH (2 × 25 mL), and H_2O (3 × 25 mL), once with brine, and dried over sodium sulfate. Removal of the solvent gave a crude oil, **1c**.

To the crude **1c** in 3 mL of MeOH was added 3 mL of a methanol–sulfuric acid solution (25 mL/g). The mixture was transferred to a separatory funnel and 25 mL of H_2O added. The cloudy solution was extracted with CH_2Cl_2 (3 × 25 mL), back-extracted with H_2O (3 × 25 mL), once with brine, and dried over sodium sulfate, and the solvent was removed to give a crude salt. The salt was recrystallized from a CH_2Cl_2–pentane system to give 87.5 mg (73%) of **1c**: mp 134–135 °C; NMR ($CDCl_3$) δ 2.13 (s, 3 H); IR (KBr) 1732, 1242 cm^{-1}; MS *m/e* 495 (M^+).

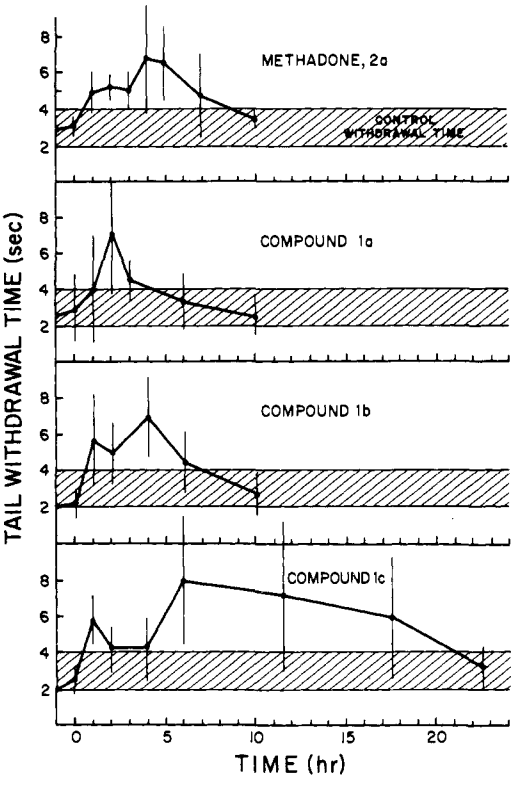

Figure 1. Duration of analgesic action following oral administration of methadone (22.5 mg/kg), **1a** (0.13 mg/kg), **1b** (0.25 mg/kg), and **1c** (0.20 mg/kg). Values shown are mean ± SEM of seven to nine animals.

Pharmacological Method. Male Sprague–Dawley rats, 180–240 g, were used in all experiments. A typical experiment consisted of ten animals. The animals were fasted 12 h prior to administration of the test compound. The animals were weighed, the lower 5-cm portion of the tail was marked with ink, and then each animal was placed in a tubular plastic cage with its tail exposed. Control tail withdrawal reaction times for each animal were determined by immersing the lower 5-cm portion of the tail in a beaker filled with water (55 °C) from a constant-temperature water bath until the tail withdrawal response was observed. The dose was prepared in such a manner so that each animal received 1 mL of solution consisting of the test compound dissolved in EtOH, Emulphor EL-719,[9] and H_2O (1:1:8). Response times were measured with an electric timer and recorded to the nearest 0.5 s. Mean control reaction time was 3.0 ± 1.0 s. Administration

of vehicle without drug had no significant effect on the reaction time. The animal was considered to be analgesic if it exhibited a response greater than 4 s. If the animal did not respond in 15 s, the tail response was considered to be completely inhibited and the warm water was withdrawn. Subsequent measurements were taken until the animal elicited normal response.

Acknowledgment. Our thanks to Janssen Pharmaceutica, who kindly furnished a sample of ketone **1a**.

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Synthesis and Pharmacological Activity and Some Derivatives of 1-Phenyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one

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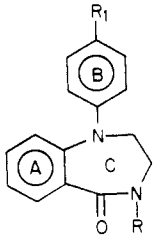
4-*N*-Alkylamino derivatives and corresponding ammonium quaternary salts of tetrahydro-1,4-benzodiazepin-5-one were synthesized and evaluated for psychotropic activity in mice by ip via. This study was also extended to some nitro and amino derivatives of tetrahydro-1,4-benzodiazepin-5-one. Compounds were devoid of tranquilizing activity and in comparison with two classical benzodiazepines, chlordiazepoxide and diazepam, they showed high toxicity and little or no effect on motor coordination, motor activity, and maximal electroshock. On some "in vitro" tests the compounds exhibited pharmacological properties when they were used at high concentrations.

At present a high number of molecules which belong to the class of 1,4-benzodiazepines are well known for their activity on the central nervous system.[1] In general, the sedative and tranquilizing activity of these compounds is such that their use in therapeutics is widespread. The compounds synthesized in our laboratories belong to the 1,4-benzodiazepine class (see structure A).



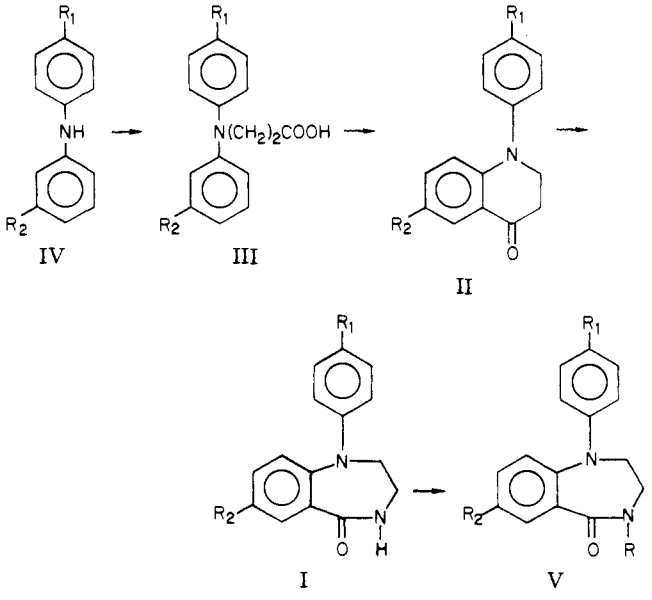
A

All the molecules possess the carbonyl group in position 5 and one phenyl group in position 1. In some cases the nitrogen atom in position 4 has been alkylated; the introduced side chain, linear or branched, contains at least 2 carbon atoms and either one aliphatic tertiary nitrogen atom or one which is part of a saturated heterocycle; the latter nitrogen atom may also be quaternized with methyl iodide. In some molecules nitro and amino groups have been introduced into rings A and B.

Chemistry. Compound I ($R_1 = R_2 = H$), from which most of the molecules described in this paper are derived, was prepared by starting from 1-phenyl-1,2,3,4-tetrahydroquinolin-4-one (II, $R_1 = R_2 = H$) by means of the Schmidt reaction under the conditions described by Misiti et al.[2] II was in turn prepared from diphenylamine in accordance with the general method described by Atwal et al.[3] for the preparation of tetrahydroquinolones (sequence IV → III → II, Scheme I).

The compounds studied in our laboratories are essentially *N*-alkylamino derivatives of benzodiazepinone I which are obtained by N-alkylation with ω-bromoalkyl tertiary amines[4] in the presence of sodium amide[5,6]

Scheme I



(compounds **1–6**, Table I). The latter, after treatment with methyl iodide,[7] gives the corresponding quaternary ammonium salts (compounds **7–12**, Table I).

In particular, the above compounds have the general formula V in which R represents the substitutions shown in Table I. The nitration of the starting quinolinone II ($R_1 = R_2 = H$) brings about the preferential formation of a dinitro derivative (II, $R_1 = R_2 = NO_2$) with nitro groups in the two aromatic rings, i.e., in position 6 and in position 4′. The structure of the dinitroquinolinone II ($R_1 = R_2 = -NO_2$) was assigned mainly on the basis of NMR data. Indeed, in the aromatic region of the NMR spectrum, a quartet of an AA′BB′ system at δ 8.03 (J_{AB} = 9 Hz), integrated for four protons, is present. This quartet should be assigned to the protons of a para-substituted aromatic ring bonded to the nitrogen atom.

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