Experimental Section[18]

10[3-(3-Azaspiro[5.5]undecan-3-yl)propyl]phenothiazine Hydrochloride (1).—10-(3-Chloropropyl)phenothiazine[19] (5 g, 0.018 mole) and 3-azaspiro[5.5]undecane[13] (5.6 g, 0.036 mole) were refluxed for 24 hr in 30 ml of toluene containing a few crystals of KI. The mixture was cooled, diluted with 2 vol of ether, and allowed to stand overnight at 5°. Precipitated **3-azaspiro[5.5]undecane hydrochloride**[13] was removed by filtration, washed with ether, and dried at 90°. It weighed 3.4 g, the theoretical amount. The filtrate was stripped at the water pump and then all material boiling up to 100° (0.2 mm) was removed at the vacuum pump and discarded. The residual oil was dissolved in 500 ml of absolute ether and saturated with HCl gas. The hydrochloride of the product was filtered, washed with ether, and dried at 90°. There was obtained 6 g (78%), mp 225–227 and 227–228°, after recrystallization from acetone–methanol–ether mixture.

10-[2-(8-Azaspiro[4.5]decan-8-yl)propyl]phenothiazine Hydrochloride (5).—10-(2-Bromopropyl)phenothiazine (mp 126–127°, 9.6 g, 0.03 mole), 8-azaspiro[4.5]decane[13] (8.4 g, 0.06 mole), and a few crystals of KI were refluxed for 30 hr in 100 ml of toluene. The cooled reaction mixture was diluted with 3 vol of ether and kept overnight at 5°. **8-Azaspiro[4.5]decane hydrobromide**[13] (5 g, theory 6.6 g) was removed by filtration and washed with ether. The filtrate and washings were stripped of solvent at the water pump until a viscous oil remained. All material boiling up to 100° (0.2 mm) was distilled; the residual oil was dissolved in 500 ml of ether and saturated with HCl gas. After filtering and drying the title compound, 8 g (65%) was obtained. It melted at 228–230° dec and at 232–234° dec after recrystallization from acetone–ether.

2-Chloro-10-[3-(3-azaspiro[5.5]undecan-3-yl)propyl]phenothiazine Hydrochloride (7).—2-Chlorophenothiazine (11.7 g, 0.05 mole) was dissolved in 50 ml of dimethylformamide and 2.6 g of a 55% suspension of NaH in mineral oil[20] was added. The mixture was heated to 50° and stirred until the evolution of hydrogen ceased. 3-(3-Chloropropyl)-3-azaspiro[5.5]undecane[13] (11.5 g, 0.05 mole) was added dropwise with stirring. The reaction mixture was maintained at 50° for 6 hr and poured into 500 ml of ice water. An oil separated which was washed by decantation several times with water. The purple oil that remained was dissolved in acetone, treated with decolorizing carbon, and filtered, and the solvent was evaporated. The residual light pink oil was dissolved in absolute ethanol and saturated with HCl gas, and several volumes of ether were added. An oil separated which slowly crystallized on slurrying with absolute ether. The product, 12 g (52%), melted at 205–206°, unchanged on recrystallization (slow) from acetone.

10-[3-(4-Methyl-4,7-epoxyhexahydroisoindolin-2-yl)propyl]-phenothiazine Hydrochloride (10).—A mixture of 10-(3-chloropropyl)phenothiazine (10 g, 0.036 mole), 4-methyl-4,7-epoxyhexahydroisoindoline[16] (11.1 g, 0.072 mole), and a few crystals of KI was refluxed for 2 days in 100 ml of toluene, and one-half of the toluene was distilled. The mixture was cooled, diluted with 3 vol of ether, and kept overnight at 5°. Precipitated **4-methyl-4,7-epoxyhexahydroisoindoline hydrochloride**[16] was removed by filtration (5.7 g, theory 6.8 g). The filtrate was evaporated until an oil remained. All material distillable up to 100° (0.2 mm) was removed from the residue and discarded. The residual oil was dissolved in ether and saturated with HCl gas to give the title compound, 9.6 g (62%), mp 124–127°. After two recrystallizations from ethylene chloride–ether, the material melted at 128–130° and softened around 114°.

(18) All melting points were taken in a Thomas–Hoover capillary type apparatus except the hydrate salt **9** which was taken on a Fisher-Johns block. Melting points are corrected. Elemental microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

(19) The commercial product is a dark, partly solid partly liquid mass. A specially purified material, pale yellow, mp 65–69°, prepared by repeated recrystallization from benzene–hexane and treated with decolorizing carbon, was used in these syntheses.

(20) Obtained from Metal Hydrides, Inc., Beverly, Mass.

Benzocyclobutene Derivatives. Oximes with Muscle Relaxant Characteristics[1]

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A number of 1-acylbenzocyclobutenes, their oximes, and several oxygen-substituted oximes were prepared and screened for potential mephenesin-like muscle relaxant activity. The compounds were obtained from a common precursor, 1-cyanobenzocyclobutene, which was made from *o*-chlorohydrocinnamonitrile by an improved method. The most effective material in the tests employed was the oxime of 1-acetylbenzocyclobutene, which was comparable in milligram potency to the comparative standard, chlorzoxazone.

To date, our study of the biological properties of compounds containing the bicyclo[4.2.0]octa-1,3,5-triene ring system has included the preparation of several 1-aminomethyl-[2] and various 1,1-disubstituted benzocyclobutenes.[3] Since skeletal muscle relaxant activity had been reported for the oximes of 2-acetyl-1,4-benzodioxane[4] and dicyclopropyl ketone,[5] compounds containing a carbonyl group adjacent to a cycloalkyl ring, a number of 1-acylbenzocyclobutenes and their oximes were made for screening as potential muscle relaxants. Several oxygen-substituted derivatives of one of the more interesting materials, 1-acetylbenzocyclobutene oxime, also were prepared. The synthesis and pharmacological evaluation of these compounds are described in the present report.

The ketones were made from 1-cyanobenzocyclobutene (**1**), which was prepared as shown in Scheme I. *o*-Chlorohydrocinnamonitrile (**2**), obtained in an overall yield of 53% from *o*-chlorobenzyl chloride and methyl cyanoacetate, was converted to **1** by a modification of the procedure of Bunnett and Skorcz.[6] This

(1) Presented in part before the Division of Medicinal Chemistry, 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966.

(2) J. A. Skorcz and J. E. Robertson, *J. Med. Chem.*, **8**, 255 (1965).

(3) J. A. Skorcz and F. E. Kaminski, *ibid.*, **8**, 732 (1965).

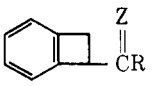
(4) C. I. Judd, J. Freedman, and J. E. Robertson, Abstracts, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, p 22N.

(5) L. E. Blockus, G. M. Everett, and R. K. Richards, *Federation Proc.*, **17**, 350 (1958).

(6) J. F. Bunnett and J. A. Skorcz, *J. Org. Chem.*, **27**, 3836 (1962).

TABLE I

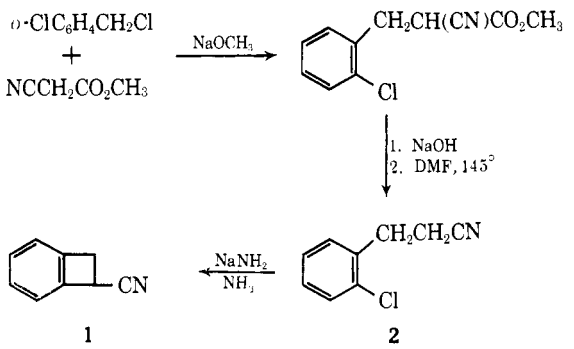
1-BENZOCYCLOBUTENYL KETONES AND OXIMES



No.	R	Z	Bp (mm) or mp, °C	Yield, %	Formula	Calcd, % C	H	N	Found, % C	H	N
4	CH_3	O	79–80 (0.9)	57	$C_{10}H_{10}O$	82.15	6.89		81.88	7.03	
5	CH_3	NOH	90–92[a]	49	$C_{10}H_{11}NO$	74.53	6.88	8.69	74.32	6.82	8.57
6	n-C_4H_9	O	93–94 (0.2)	56	$C_{13}H_{16}O$	82.94	8.56		82.88	8.49	
7	n-C_4H_9	NOH	55–58[a]	27	$C_{13}H_{17}NO$	76.80	8.43	6.89	76.82	8.22	6.88
8	C_6H_5	O	124–126 (0.04)[b]	50	$C_{15}H_{12}O$	86.51	5.81		86.32	5.90	
9	C_6H_5	NOH	131–134[c]	31	$C_{15}H_{13}NO$	80.69	5.87	6.27	80.49	6.17	6.34
10	$CH_2C_6H_5$	O	133–134 (0.1)	30	$C_{16}H_{14}O$	86.45	6.35		86.40	6.45	
11	$CH_2C_6H_5$	NOH	87–90[d]	18	$C_{16}H_{15}NO$	80.98	6.37	5.90	81.07	6.27	5.82
12	C_6H_{11}	O	98–102 (0.005)	25	$C_{15}H_{18}O$	84.07	8.47		83.88	8.45	
13	C_6H_{11}	NOH	187–188[e]	28	$C_{15}H_{19}NO$	78.56	8.35	6.11	78.74	8.55	5.96
14	C_3H_5	O	87–100 (4.5)[f]	19	$C_{12}H_{12}O$						
15	C_3H_5	NOH	127–131[g]	10	$C_{12}H_{13}NO$	76.97	7.00	7.48	76.55	7.09	7.65

[a] Crystallized from Skellysolve B (bp 60–80°). [b] Solidified on standing, mp 75–77.5° after recrystallization from aqueous methanol. [c] Appreciable prior softening. [d] Crystallized from aqueous methanol. [e] Crystallized from chloroform–ethanol. [f] Cyclopropyl ketone, contaminated by starting nitrile, was converted directly to oxime. [g] Crystallized from cyclohexane.

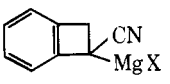
SCHEME I



1 2

benzyne-mediated cyclization was conveniently carried out with up to 3 moles of **2** in yields of 62–70%.

The carbonyl compounds were obtained from **1** by way of reaction with the appropriate Grignard reagents. Although optimum conditions were not determined, a moderate (40–150%) excess of the organometallic reagent was sufficient, in most cases, to provide the 1-benzocyclobutenyl ketone in fair yield.[7] Since removal of the α hydrogen of **1** is facile,[3] proton abstraction by the Grignard reagent to afford an intermediate equivalent to **3** probably was a competing



3

reaction. This was suggested by the recovery of some starting nitrile from all of the reactions;[8] the maximum amount was 35% in the case of the usually sluggish cyclohexylmagnesium bromide.

The oximes in Table I were prepared in the usual fashion with a slight excess of hydroxylamine in aqueous ethanol. The crude yields generally were high, but invariably only a portion of the material could be induced to crystallize as a sharp-melting solid. Although this behavior implied the presence of both the *syn*- and *anti*-ketoximes, no attempt was made to isolate the isomeric compounds.

Two general methods were utilized to obtain the O-alkyl oximes in Table II. The condensation of 1-acetylbenzocyclobutene (**4**) with methoxyamine and *n*-butyloxyamine afforded **16** and **17**, respectively. Since this approch was limited by the availability of the alkoxyamines, the oxime **5** was alkylated directly. Treatment of **5** with sodamide in dimethylformamide at ambient temperature, followed by the introduction of a suitable alkyl halide, provided the ketoxime ethers **16, 18,** and **19.** Hydroxyalkylation of **5** with propylene oxide yielded the carbinol **20**; assignment of the secondary alcohol structure was made on the basis of similar reactions described in the literature.[9]

Contrary to the reported acylation of dicyclopropyl ketoxime,[10] heating the oxime **5** in acetic anhydride resulted in extensive decomposition. The use of acetyl chloride in ether, however, readily gave the ester **21.**

The structural integrity of the bicyclic ring system in each of the compounds was substantiated by ultraviolet (λ_{max} near 272, 265, and 260 mμ) and infrared (cycloalkyl band at 10.0–10.1 μ) spectra.[3] All of the O-substituted oximes displayed weak C=N absorption near 6.1 μ, and, in addition, the ethers had a strong C–O band at approximately 9.6 μ.

Pharmacology.—The benzocyclobutene derivatives were evaluated for possible and relative mephenesin-like central muscle relaxant activity by two primary methods with chlorzoxazone as a standard. Results for the three types of compounds are summarized in Table III.

In spinal cats, it was observed that of the ketones the alkyl (**4** and **6**) and aryl (**8**) compounds produced a slight selective polysynaptic block at the lower doses but were toxic at the higher dose levels. In contrast with this, the benzyl group (**10**) produced a reverse

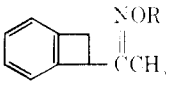
(7) C. Kaiser and C. L. Zirkle, U. S. Patent 3,149,159 (1964), synthesized ketone **4** from benzocyclobutene-1-carboxylic acid and excess methyllithium; no yield was given. The oxime **5** also was mentioned.

(8) Similar results have been reported for reactions of phenylacetonitrile with various Grignard reagents; at best, small amounts of the expected ketones were formed, presumably because of preferential attack at the reactive methylene protons. For example, see C. R. Hauser and W. J. Humphlett, *J. Org. Chem.*, **15**, 359 (1950); W. I. O'Sullivan, F. W. Swamer, W. J. Humphlett, and C. R. Hauser, *ibid.*, **26**, 2306 (1961).

(9) G. B. Bachman and T. Hokama, *J. Am. Chem. Soc.*, **81**, 4223 (1959).

(10) B. W. Horrom, U. S. Patent 3,117,987 (1964).

TABLE II
O-SUBSTITUTED OXIMES OF 1-ACETYLBENZOCYCLOBUTENE



No.	R	Bp (mm), °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
16	CH_3	48–49 (0.05)	60	$C_{11}H_{13}NO$	75.39	7.48	7.99	75.18	7.70	7.76
17	n-C_4H_9	93–94 (2.3)	48	$C_{14}H_{19}NO$	77.38	8.81	6.45	77.51	9.03	6.38
18	$CH_2C_6H_5$	137–139 (0.95)	33	$C_{17}H_{17}NO$	81.24	6.86	5.57	81.56	6.72	5.39
19	$CH_2CH{=}CH_2$	76–78 (0.05)	88	$C_{13}H_{15}NO$	77.58	7.51	6.96	77.71	7.59	6.78
20	$CH_2CH(OH)CH_3$	84–85 (0.1)	87	$C_{13}H_{17}NO_2$	71.25	7.81	6.39	71.35	7.97	6.46
21	$COCH_3$	114–115 (0.02)	72	$C_{12}H_{13}NO_2$	70.92	6.44	6.89	70.95	6.46	6.91

TABLE III
EFFECT ON SPINAL CAT REFLEX AND MOUSE BEHAVIORAL PROFILE

Compd	Spinal cat: Inhibition of Poly-synapse[a]	Spinal cat: Inhibition of Mono-synapse[a]	Mouse behavioral profile: Muscle relaxant activity[b]	Mouse behavioral profile: Other activity[c]	Approx LD_{50}, mg/kg
Std[d]	++++	+ (?)	+++	T	550
4	++	±	++	0	550
6	+	0	+	S	550
8	+	0	+	0	1250
10	S	0	0	S	1750
12	0	0	+ (?)	T	>1000
5	++++	0	+++	T	550
7	++	0	+	S (?)	550
9	+	0	+	S	>3000
11	S	S	+ (?)	S	550
15	+++	+ (?)	+	S	>1000
16	+++	0	+++	T	550
17	0	0	0	D	1750
18	+ (?)	0	0	D	>3000
19	+	0	+	T	1320
20	+++	+	+	0	550
21	+++	+	++	0	550

[a] Scoring of relative synaptic reflex inhibition on 0 to 4+ basis; S = a reverse effect (stimulation). [b] Scoring of relative muscle relaxant activity on 0 to 3+ basis. [c] S = stimulation, T = tranquilizing activity, D = depression at high doses, 0 = no activity. [d] Standard compound, chlorzoxazone (Paraflex®).

effect in that it induced an increase in polysynaptic reflex activity. The cyclohexyl ketone **12** was without effect on the reflexes.

A similar relationship was evident with the oximes.[11] The methyl (**5**) and cyclopropyl (**15**) compounds produced polysynaptic reflex inhibition with a relatively high degree of selectivity and potency. Increasing the length of the alkyl chain (**7**) reduced the activity, but also increased the relative toxicity. Aryl substitution (**9**) resulted in very weak but selective inhibitory activity. As was seen with the parent ketone **10**, the presence of a benzyl group (**11**) produced a stimulatory effect. In contrast with the former, the increase in the polysynaptic reflex activity was very pronounced, with a slight concomitant increase in the monosynaptic reflex.

In the case of the O-substituted oximes, methyl (**16**), hydroxypropyl (**20**), or acetyl (**21**) substitution of the parent compound **5** resulted in but a slight decrease in the degree of polysynaptic blockade. However, the introduction of a higher alkyl (**17**), benzyl (**18**), or vinyl (**19**) substituent resulted in an apparent complete loss or a considerably reduced activity.

Thus, the most effective compound in this test, and comparable with chlorzoxazone in milligram potency, was 1-acetylbenzocyclobutene oxime (**5**).

It is of further interest that essentially similar structure–activity relationships were observed with these compounds in their mouse behavioral profiles (Table III). However, it may also be seen that several of the compounds (**5**, **12**, **16**, and **19**) induced activity suggesting tranquilization. There was no apparent structure–activity relationship in this pharmacologic classification.

Experimental Section[12]

Methyl *o*-Chlorobenzylcyanoacetate.—To a stirred solution of 63.1 g (1.17 moles) of commercial sodium methoxide and 454 g (4.58 moles) of methyl cyanoacetate in 800 ml of methanol at 25° was added 184 g (1.15 moles) of α,*o*-dichlorotoluene over a 1-hr period. The resulting milky solution was refluxed for 3 hr, and the solvent was removed under vacuum. The residue was taken up in ether, which was washed with water, dried (Na_2SO_4), and evaporated. The excess cyano ester was distilled, followed by 150 g (59%) of product as a colorless liquid, bp 126–127° (0.75 mm), which readily solidified on standing. A sample melted at 54–57° after recrystallization from 2-propanol.

Anal. Calcd for $C_{11}H_{10}ClNO_2$: C, 59.08; H, 4.51; Cl, 15.86; N, 6.27. Found: C, 59.00; H, 4.59; Cl, 15.81; N, 6.23.

***o*-Chlorobenzylcyanoacetic Acid.**—To a cooled solution of 10% NaOH (750 ml) was added with stirring 136 g (0.61 mole) of methyl *o*-chlorobenzylcyanoacetate, as a melt. After 15 min the solution was diluted with water (250 ml) and acidified with concentrated HCl (200 ml). The resulting mixture was stirred for 1 hr, and the precipitated material was filtered, washed well with water, and dried to give 128 g (100%) of the cyano acid, mp 130–132° (lit.[13] mp 134–135.5°).

***o*-Chlorohydrocinnamonitrile (2).**—The cyano acid (128 g, 0.61 mole) in 100 ml of dimethylformamide (DMF) was decarboxylated as described for a related compound.[2] Distillation afforded 88.5 g (89%) of the nitrile, bp 85° (0.3 mm), lit.[14] bp 140–145° (15 mm), n^{25}D 1.5362.

1-Cyanobenzocyclobutene (1).—To a well-stirred suspension of commercial sodamide (312 g, 8 moles) in 5 l. of liquid ammonia under nitrogen was added 331 g (2 moles) of the nitrile **2** over a 10-min period. The mixture was stirred for 3 hr, neutralized with solid NH_4NO_3, and allowed to stand until the ammonia had evaporated (overnight). Water was cautiously added to the residue, and the organic material was taken up in chloroform, which was washed twice with 5% HCl and once with water, dried (Na_2SO_4), and evaporated. Distillation of the remaining

(11) The cyclohexyl ketoxime **13** was too insoluble in propylene glycol for evaluation in the present experimental procedure.

(12) Melting points were taken with a Thomas–Hoover apparatus and are corrected. Analyses were performed in our laboratories and by Drs. G. Weiler and F. B. Strauss, Oxford, England. The ultraviolet spectra were obtained with a Beckman spectrophotometer, Model DK2A, and the infrared spectra with a Beckman spectrophotometer, Model IR 8.

(13) R. H. Garst, Ph.D. Dissertation, Brown University, 1964.

(14) A. O. Grebenyuk and I. P. Tsukervanik, *J. Gen. Chem. USSR*, **25**, 269 (1955); *Chem. Abstr.*, **50**, 1639 (1956).

liquid (301 g) afforded 179.3 g (70%) of the nitrile, bp 90–92° (3 mm), lit.[15] bp 88° (1.3 mm), n^{25}D 1.5451.

The methods used to prepare the ketones and the O-substituted oximes are illustrated by the following procedures.

1-Benzocyclobutenyl *n*-Butyl Ketone (6).—To the Grignard reagent prepared from 11.8 g (0.48 g-atom) of magnesium turnings and 65 g (0.48 mole) of 1-bromobutane in 800 ml of anhydrous ether was added dropwise a solution of 25 g (0.19 mole) of 1-cyanobenzocyclobutene (**1**) in 150 ml of ether. The mixture was stirred at room temperature for 15 hr and then was treated with 100 ml of saturated NH_4Cl solution. Water (1 l.) was added, the ether was removed by distillation, and the remaining mixture was heated at reflux for 1 hr. The cooled organic layer was taken up in ether, which was dried (Na_2SO_4) and evaporated. Distillation of the residue afforded 0.7 g (3%) of the starting nitrile, followed by 20.6 g of the ketone as a colorless liquid. A portion was redistilled for analysis; λ_{max}^{EtOH} 273 mμ (ε 1350), 266 (1520), 260 (1230), and a shoulder at 254 (1000). Infrared bands appeared at 5.87 and 10.04 μ (CS_2).

O-Methyl-1-acetylbenzocyclobutene Oxime (16). Alkylation Method.—A mixture of the oxime **5** (9.0 g, 0.056 mole) and 2.4 g (0.062 mole) of sodamide in 25 ml of DMF was stirred at room temperature for 18 hr, then heated for 1 hr at 50°, and cooled. Methyl iodide (41 g, 0.28 mole) was added, and the mixture was stirred overnight at 25°, diluted with ether (300 ml), and filtered. The filtrate was washed with water, dried (Na_2SO_4), and evaporated to afford 9.4 g of a brown liquid. Elution of this material from 200 g of alumina with Skellysolve B (bp 60–80°)–benzene (5:1) provided the product (5.8 g) as a colorless liquid. A portion was distilled for analysis; λ_{max}^{EtOH} 272 mμ (ε 1830), 265 (1890), and 259 (1250). Infrared bands appeared at 6.15, 9.51, and 10.03 μ (CS_2).

Alkoxyamine Method.—A solution of the ketone **4** (10 g, 0.07 mole) and 5.7 g (0.07 mole) of methoxyamine hydrochloride in 60 ml of pyridine was refluxed for 6 hr. The cooled solution was diluted with water and extracted with chloroform, which was washed with 2% HCl and water, dried (Na_2SO_4), and evaporated. Chromatography of the residual liquid (6.6 g) as outlined in the previous procedure afforded the oxime ether **16** in 40% yield.

O-(2-Hydroxypropyl)-1-acetylbenzocyclobutene Oxime (20).—To the anion generated from the oxime **5** (2.8 g, 0.016 mole) with 0.8 g (0.02 mole) of sodamide in 25 ml of DMF was added dropwise 9 g (0.15 mole) of propylene oxide, and the mixture was stirred overnight at 25°. Dilution with water and extraction with ether afforded 3.2 g of crude material, which was eluted from 70 g of alumina with benzene–ether (1:1). The resulting pale yellow oil amounted to 2.8 g. A portion was distilled for analysis; λ_{max}^{EtOH} 272 mμ (ε 2080), 266 (2120), and 260 (1420). Infrared bands appeared at 2.79, 2.87, 6.16, 9.62, and 10.06 μ (CS_2).

O-Acetyl-1-acetylbenzocyclobutene Oxime (21).—A cooled solution of the oxime **5** (6.4 g, 0.04 mole) and triethylamine (4 g, 0.04 mole) in 100 ml of anhydrous ether was treated dropwise with 3.2 g (0.04 mole) of acetyl chloride in ether (50 ml). The reaction mixture was stirred overnight at 25°, the amine salt was filtered and washed with ether, and the combined ether portions were evaporated. Distillation of the residue (8.5 g) afforded 5.75 g of the ester as a straw-colored liquid; λ_{max}^{EtOH} 271 mμ (ε 1890), 265 (1950), and 259 (1280). Infrared bands appeared at 5.68, 6.11, and 10.06 μ (CCl_4).

Biological Screening. Effect on Spinal Cat Reflex.—The compounds were administered to unanesthetized cats with a high spinal transection at the level of the second cervical vertebrae. The procedure employed was a slightly modified method of Slater and his associates[16] and involved determination of relative milligram potency and the degree of selective antagonism of polysynaptic spinal reflex activity, the flexor reflex, in comparison with the effect on monosynaptic activity, the patellar reflex or knee jerk. The latter was elicited with an electrically operated automatic hammer, and the response of the leg was recorded kymographically from the sectioned Achilles tendon. The flexor reflex was recorded similarly from the severed end of the anterior tibial tendon of the opposite leg following square wave stimulation of the peripherally ligated ipsilateral tibial nerve. All compounds were administered intravenously in doses of 4, 8, and 16 mg/kg in a total volume of 1 or 2 ml of propylene glycol. An occasional compound was also administered at a dose of 32 mg/kg. The rate of injection was maintained constant at 3 min for all doses. Only one experimental compound was administered to each cat. However, all animals received a final injection of chlorzoxazone as a standard for comparative purposes and to test the viability of the preparation. This was administered at a dose of 8 mg/kg and occasionally also at a dose of 16 mg/kg. Relative activity is presented in Table III as an arbitrary score of 0 to 4+.

Mouse Behavior.—The profiles were obtained essentially in accordance with the procedure outlined by Irwin.[17] This consists of gross observations of various parameters prior to, during, and following animal manipulation, both before and after drug administration. Peak effects were scored on an arbitrary scale of 0–8, with a base-line score for "normal" signs as 4 and for "abnormal" signs as 0. Summary scores presented in Table III, describing muscle relaxant and other pharmacologic areas of activity, are on a 0 to 3+ basis. Compounds that were relatively inactive, toxic, or that possessed an apparent low therapeutic ratio (therapeutic dose/LD_{50}) were given a score of 0. There were three mice at each dose level, and all agents were administered intraperitoneally in a suspension of 5% gum acacia. Approximate LD_{50} values were also obtained from these investigations.

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