(5) H. Schmitt, H. Schmitt, and S. Fenard, *Experientia*, **29**, 1247 (1973).
(6) P. Bousquet and P. G. Guertzenstein, *Br. J. Pharmacol.*, **49**, 573 (1973).
(7) R. A. Burton and A. M. Roe, English Patent 1080167; *Chem. Abstr.*, **68**, 95518r (1968).
(8) B. C. Saunders and G. H. R. Watson, *Biochemistry*, **8**, 632 (1959).
(9) E. C. Bate-Smith and R. G. Westall, *Biochim. Biophys. Acta*, **4**, 427 (1950).
(10) B. C. Boyce and B. V. Milborrow, *Nature (London)*, **5010**, 537 (1965).
(11) W. Draber, K. H. Buchel, and K. Dichore, *Proc. Int. Congr.*, **5**, 153 (1972).
(12) R. W. Taft, "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, p 556.
(13) T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, **86**, 5175 (1964).
(14) M. S. Tute, *Adv. Drug Res.*, **6**, 1 (1971).
(15) P. J. Goodford, *Adv. Pharmacol. Chemother.*, **11**, 52–96 (1973).
(16) C. Hansch and E. W. Deutsch, *Biochim. Biophys. Acta*, **126**, 117 (1966).
(17) J. C. Dearden and E. Tomlinson, *J. Pharm. Pharmacol.*, **24** (suppl.), 115 (1972).
(18) G. L. Biagi, A. M. Barbaro, M. C. Guerra, G. C. Forti, and M. E. Fracasso, *J. Med. Chem.*, **17**, 28 (1974).
(19) J. Iwasa, C. Hansch, and T. Fujita, *J. Med. Chem.*, **8**, 150 (1965).
(20) G. L. Biagi, M. G. Guerra, and A. M. Barbaro, *J. Med. Chem.*, **13**, 511, 945 (1970).
(21) J. Cymerman-Craig and A. A. Diamantis, *J. Chem. Soc.*, 1619 (1953).
(22) D. H. MacDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).
(23) H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958).
(24) C. G. Swain and E. C. Lupton, *J. Am. Chem. Soc.*, **90**, 4326 (1968).
(25) K. Starke, H. Montel, W. Gayk, and R. Merker, *Naunyn-Schmiedebergs Arch. Pharmakol.*, **285**, 133 (1974).
(26) R. E. Shipley and J. H. Tilden, *Proc. Soc. Exp. Biol. Med.*, **64**, 453 (1947).
(27) Belgium Patent 623305 (1965); *Chem. Abstr.*, **64**, 2096e (1966).
(28) Y. Kinoshita, N. Matsuda, S. Sakai, Y. Oshima, T. Harada, and T. Nishihara, *Agric. Biol. Chem.*, **30**, 447 (1966); *Chem. Abstr.*, **65**, 7081*f* (1966).
(29) L. Toldy and M. Rados, Hungarian Patent 155329 (1968); *Chem. Abstr.*, **70**, 132 (1969).
(30) G. W. Snedecor, "Statistical Methods", Iowa State University Press, Ames, Iowa, 1966.

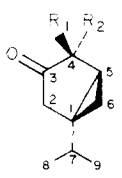
(−)-3-Isothujone, a Small Nonnitrogenous Molecule with Antinociceptive Activity in Mice

Kenner C. Rice* and Raymond S. Wilson

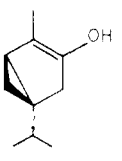
Laboratory of Chemistry, National Institute of Arthritis, Metabolism and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20014. *Received January 12, 1976*

(−)-3-Isothujone and (+)-3-thujone were examined for antinociceptive activity using the hot-plate and Nilsen tests. In the hot-plate test (−)-3-isothujone (ED_{50} = 6.5 mg/kg) was found to be codeine-like and equipotent with (−)-Δ^9-tetrahydrocannabinol while the racemic material was essentially half as potent as the levorotatory isomer. (+)-3-Thujone was inactive in both antinociceptive tests as were several structural analogues of the 3-thujones. As with the THC's less antinociceptive activity was observed in the Nilsen test than in the hot-plate assay. Acute toxicities for the 3-thujones were determined and vastly improved synthetic procedures have been developed for two long-known but difficultly accessible 3-thujanols.

The widely occurring natural products (+)-3-thujone (**1**) and (−)-3-isothujone (**2**)[1,2] are ketonic constituents of the essential oils of the two[2] *Artemisia* (family Compositae) species (*A. absinthium* L. and *A. pontica* L.) from which the alcoholic drink absinthe was prepared in France before its prohibition in 1915. In a recent report del Castillo et al.[3] compared the structure of a 3-thujone[4] and the $\Delta^{3,4}$-enol (**3**) with (−)-Δ^9-tetrahydrocannabinol (Δ^9-THC, **4**), the major psychoactive component of marihuana. One of the ketones (**1** or **2**) was credited[3] with being responsible for certain CNS effects of absinthe and based upon certain geometrical similarities in their structures, del Castillo et al.[3] suggested that this ketone or the $\Delta^{3,4}$-enol (**3**) and the THC's (or their biologically active 11-hydroxy metabolites) act at a common receptor in the CNS.



1, $R_1 = CH_3$; $R_2 = H$ (+)
2, $R_1 = H$; $R_2 = CH_3$ (−)

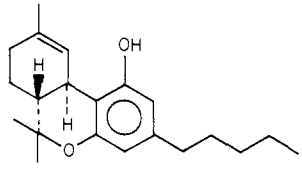


3

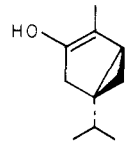
In a search for novel nonaddicting analgesics, we have examined the tetrahydrocannabinols, many of their metabolites,[5] and a considerable number of synthetic analogues.[6] Therefore it was of interest to examine **1**, **2**, and related compounds for possible antinociceptive activities.

As our initial evaluation of a commercial mixture of **1** and **2** revealed significant antinociceptive activity, determined as described below, a detailed search of the literature was made in order to determine how to best purify each of these two ketones. During this examination of the literature, we reviewed the careful work by Norin in which the relative[7] and absolute[8] stereochemistry of the 3-thujones and 3-thujanols was assigned. Later work,[9-11] including an x-ray crystal study,[12] has confirmed the assignments by Norin who showed that the absolute stereochemistry of natural (−)-3-isothujone is represented by **2** and that of its epimer, (+)-3-thujone, by **1**. The $\Delta^{3,4}$-enol of these ketones must therefore have structure **5**. Since this structure is enantiomeric with that of **3** which del Castillo et al. compared with natural (−)-Δ^9-THC, known[13] to have the absolute stereochemistry shown in **4**, it follows that the topological comparison of these authors was made between unnatural $\Delta^{3,4}$-thujone enol (**3**) and natural Δ^9-THC (**4**). Because of this situation and the

biological results described below, we became interested in preparing a sample of racemic 3-isothujone (6) for comparison of its antinociceptive activity with that of the natural material.



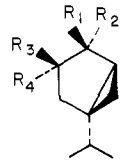
4



5

Chemistry. Distillation of Western Red Cedar leaf oil (*Thuja plicata* Donn), which is known[14] to contain 5–10% of (+)-3-thujone (1) and 70–80% of (−)-3-isothujone (2), gave, after an easily separable terpene fraction, approximately 80% weight yield of a mixture consisting of 1 and 2 in a ratio of ~8:92. This mixture was used directly for the preparation of pure 2 and derivatives as described below. Although the isomer ratio was favorable, initial work aimed at complete purification of 2 by direct distillation using a spinning-band column proved difficult and time consuming. Consequently, an alternate method of purification through *crystalline* (−)-3-neoisothujanol (7) was investigated.

Pure (−)-3-isothujone (2) has previously[15] been obtained by oxidation of this alcohol. However, purification of the alcohol has required a tedious fractional distillation,[7] 12 recrystallizations of a derivative,[15] or preparative GLC.[16] Goryaev[17] has reported that Meerwein–Ponndorff–Verley (MPV) reduction of 2 provided approximately equal amounts of 7 and (+)-3-thujanol (8). However, these results are in disagreement with those of Banthorpe,[16] whose nonpreparative, product ratio studies of the reduction of 1 and 2 with several reagents indicated that MPV reduction of 2 gave an 87:13 ratio of (−)-3-neoisothujanol (7) to (−)-3-isothujanol (9). Kinetic studies of this reduction by Hach[18] have subsequently confirmed the identity of the products reported by Banthorpe and the high ratio of 7 to 9. Utilizing these observations we have developed a simple preparative procedure for pure 7, in any desired quantity, by MPV reduction of the readily available ketone mixture described above. This method furnished the desired alcohol 7 (in 47% yield) which was easily isolated by direct crystallization. Brown[19] oxidation of this alcohol then provided pure 2.

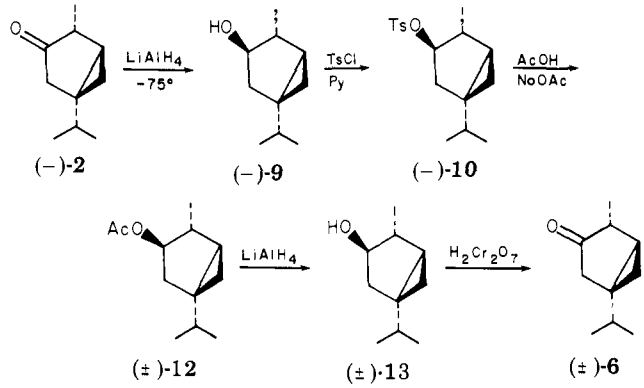


7, R_1 = H; R_2 = CH_3; R_3 = H; R_4 = OH (−)
8, R_1 = CH_3; R_2 = R_3 = H; R_4 = OH (+)
11, R_1 = H; R_2 = CH_3; R_3 = H; R_4 = OTs (−)
14, R_1 = H; R_2 = CH_3; R_3 = *p*-$NO_2C_6H_4CO_2$; R_4 = H (−)
15, R_1 = H; R_2 = CH_3; R_3 = *p*-$NO_2C_6H_4CO_2$; R_4 = H (±)

Pure 1 was obtained as previously described[14] from the ketone mixture by base-catalyzed equilibration to the 2:1 equilibrium mixture of 1 to 2, isolation of 1 as the bisulfite adduct, and regeneration of the pure ketone.

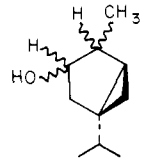
For the racemization of (−)-3-isothujone (2) we have utilized the observation made by Norin[20] during kinetic work that acetolysis of (−)-3-isothujanol *p*-toluenesulfonate (10) but not (−)-3-neoisothujanol *p*-toluenesulfonate (11) gave racemic 3-isothujyl acetate (12). Although the acetate was reported to have been reduced to racemic 3-isothujanol (13), neither physical constants for the intermediates nor the final product in this sequence were reported. We have confirmed this report and have developed the following preparative method (Scheme I) for racemic 3-isothujone (6). Low-temperature (−75°) $LiAlH_4$ reduction of the ketone mixture described above proceeded with high stereospecificity, as reported by Banthorpe[16] in his product-distribution studies, to give an alcohol mixture from which pure (−)-3-isothujanol (9) was easily isolated through the crystalline (−)-*p*-nitrobenzoate 14. Reaction of this alcohol with excess *p*-toluenesulfonyl chloride, although a slow reaction, gave the moderately stable tosylate 10 in high yield. Acetolysis of the tosylate gave the oily acetate 12 along with a minor unidentified side product. $LiAlH_4$ reduction of the crude acetate furnished racemic 3-isothujanol 13 which was easily purified through the *p*-nitrobenzoate 15. Brown[19] oxidation of the racemic alcohol (13) provided racemic 3-isothujone (6) which, except for optical rotation, was identical with natural (−)-3-isothujone (2).

Scheme I. Racemization of (−)-3-Isothujone

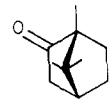


(−)-2 (−)-9 (−)-10 (±)-12 (±)-13 (±)-6

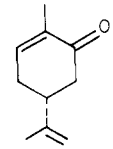
Biological Results. Antinociceptive testing was performed using male, white mice in the hot-plate[21] and Nilsen test[22] by the usual methodology. The compounds tested here were given subcutaneously (sc) as suspensions in Emulphor (El-620),[23] ethanol, and saline.[24] The vehicle was inactive in all tests.[5] To examine the specificity of (−)-3-isothujone (2) in these tests we have also examined (±)-3-isothujone (6), (+)-3-thujone (1), (−)-3-neoisothujanol (7), (−)-3-isothujanol (9), a commercial diastereoisomeric mixture of the four 3-thujanols (16), *d*-camphor (17), and *l*-carvone (18), all of which have structures similar to 2.



16



17



18

The results are compared with those of several cannabinoids we have tested previously[5] and morphine and codeine. As indicated in Table I, 2 is essentially equipotent with codeine and Δ^9-THC (4) in the hot-plate test. Racemic 3-isothujone (6) was approximately half as active as 2 in this test, suggesting that most or all of the activity is due to the (−) isomer. When 2 was epimerized at C-2, the resulting (+)-3-thujone (1) was inactive except at much higher doses where infrequent convulsions also occurred. In the Nilsen test, 2 was about half as active as in the hot-plate test like the cannabinoids, tested previously.[5] In contrast, the opiates are usually of comparable potency in these two tests.[22] Except for the slight activity of the alcohol 9, none of the related compounds tested had

Table I. Antinociceptive Potencies of (−)-3-Isothujone and Other Compounds[a]

Compound	Hot-plate ED_{50}, mg/kg sc[a]	Nilsen ED_{50}, mg/kg sc[a]	LD_{50}, mg/kg sc[a]
(+)-3-Thujone (1)	Marginally act. at 100	Marginally act. at 100	442.2 (356-548.4)
(−)-3-Isothujone (2)	6.5 (4.3-8.8)	14.1 (8.9-22.5)	87.5 (73.0-104.9)
(±)-3-Isothujone (6)	16.7 (12.7-22.1)		134.2 (121.6-148.0)
(−)-3-Neoisothujanol (7)	Inact. at 50		
(−)-3-Isothujanol (9)	33.3 (21.6-51.4)		
Thujanols (16)[b]	Inact. at 100		
(−)-Δ^9-THC (4)	9.6 (7.4-12.5)		
(−)-Δ^8-THC	8.8 (6.2-12.5)	Essentially Inact. at 20	
(−)-11-Hydroxy-Δ^8-THC	1.9 (1.4-2.7)	5.4 (3.2-8.9)	
d-Camphor (17)	Inact. at 100		
l-Carvone (18)	Inact. at 100		
Morphine sulfate	1.2 (0.9-1.3)	0.8 (0.6-1.2)	576 (558-594)
Codeine hydrochloride	7.5 (6.7-8.3)	4.5 (2.7-7.6)	270 (262-278)
(±)-Methadone	0.80 (0.64-1.0)		44 (43-45)

[a] The ED_{50}'s were determined using four doses and ten mice per dose. Numbers in parentheses are the 95% confidence limits obtained by probit analyses. The room temperature was 23 °C for determination of ED_{50}'s and LD_{50}'s. [b] A diasteroisomeric mixture of the four 3-thujanols was purchased from K and K Laboratories, Plainview, N.Y.

appreciable antinociceptive activity.

Using the same strain of mice, vehicle, and route of administration used for the antinociceptive evaluation, the LD_{50} for (−)-3-isothujone (2) was found to be 87.5 (73.0–104.9) mg/kg. Racemic 3-isothujone (6) was essentially half as toxic as 2 while (+)-3-thujone (1) showed an LD_{50} of 442.4 (356.6–548.4) mg/kg. Infrequently, convulsions were observed at 50 mg/kg (none at 40 mg/kg or below) for 2 and at 100 mg/kg for (+)-3-thujone (1).

Although the data presented in this paper do not distinguish whether (−)-3-isothujone (2) acts at the same site in the CNS as the THC's a novel, simple, nonbasic chemical structure which can produce antinociceptive activity in mice is reported and this would appear to merit further investigation. The combination of both structural and stereospecificity in the antinociceptive activity of (−)-3-isothujone (2) is suggestive of a specific receptor interaction. If the $\Delta^{3,4}$-enol form of the 3-thujones is the active form as suggested by del Castillo et al.,[3] then 1 and 2 might be expected to have similar antinociceptive potencies inasmuch as they share this common enol (5) (pure samples of either are readily converted to the same equilibrium mixture of both compounds). Our data suggest, therefore, that the enol is not an important contributing structure in the antinociceptive activity of (−)-3-isothujone (2) in mice. This assumes, however, a similar rate of enolization and formation of the same enol ($\Delta^{3,4}$, 5) in vivo by (+)-3-thujone (1) and (−)-3-isothujone (2).

Experimental Section

Melting points (corrected) were determined in open capillary tubes. Optical rotations were measured with a Cary 60 recording spectropolarimeter at 589 nm, using the solvents and concentrations specified. Microanalyses, performed by the Laboratory's Section on Microanalytical Services and Instrumentation, are within ±0.3% of the calculated values. Silica gel 60 for chromatography was purchased from EM Laboratories, Inc., Elmsford, N.Y. Ir (Perkin-Elmer 257), NMR (Varian A-60 or HR-220), and mass (Hitachi Perkin-Elmer RMU-6E for electron ionization or Finnigan 1015D with a model 6000 data-collection system for chemical ionization) spectra were consistent with the expected structures. Gas–liquid chromatography (GLC) was done on a Beckman GC-55 using a 5% XE-60 on Chromosorb W column.

Partial Purification of (−)-3-Isothujone (2) from Cedar Leaf Oil. Distillation of Western Red Cedar (*Thuja plicata* Donn) leaf oil (100 g) using a spinning-band column gave a terpene fraction (10.3 g), bp 30–84° (20 mm), and 81.3 g of material, bp 84–87° (20 mm), consisting of ca. 8% (−)-3-thujone (1) and 92% (−)-3-isothujone (2) (GLC).

(−)-3-Neoisothujanol (7). The following preparative procedure was developed based on the observations of Banthorpe.[16] The ketone mixture (15.2 g, 0.1 mol) from above was added to a solution of freshly distilled aluminum isopropoxide (25.0 g, 0.12 mol) in dry 2-PrOH (225 ml). Using a spinning-band column, the solution was slowly and continuously distilled to remove acetone produced in the reduction while adding several portions of dry 2-PrOH to maintain a volume of ~250 ml. After 2.5 h when GLC indicated the starting ketones were consumed, the batch was concentrated to ~0.5 vol in vacuo and poured into a mixture of Et_2O (200 ml) and ice (200 g). Sufficient cold, 10% HCl was added to dissolve most of the inorganic material, the Et_2O was separated, and the aqueous layer extracted with additional Et_2O (2 × 100 ml). The combined Et_2O extract was washed successively with 5% NaOH and brine, dried ($MgSO_4$), evaporated, and distilled to give 14.5 g (94%) of a colorless oil, bp 75–80° (5 mm). Crystallization and recrystallization from hexane (cooling to −75°) gave 7.3 g (47%) of pure 7: mp 68–69°; $[\alpha]^{23}D$ −23.9° (*c* 2.46, EtOH) [lit.[7] mp 66–7°; $[\alpha]^{23}D$ −24° (*c* 2.3, EtOH)].

(−)-3-Isothujone (2). Brown[19] oxidation of 7 (4.5 g, 0.029 mol) from above, followed by chromatography over silica gel 60 using *i*-$(Pr)_2O$–hexane (1:1), and distillation gave 3.8 g (86%) of pure 2: bp 83–84° (20 mm); $[\alpha]^{23}D$ −20.2° (neat) [lit.[15] bp 74–75° (9 mm); $[\alpha]D$ −19.94° (neat)].

(+)-3-Thujone (1). The ketone mixture from above was treated as previously described[14] to give pure 1: bp 83–84° (20 mm); $[\alpha]^{23}D$ +78.1° (neat) [lit.[14] bp 40.9° (0.5 mm); $[\alpha]^{25}D$ +78.8° (neat)].

(−)-3-Isothujanol (9). The ketone mixture (15.2 g, 0.1 mol) in Et_2O (150 ml) was added dropwise to a slurry (under N_2) of $LiAlH_4$ (9.48 g, 0.25 mol) in Et_2O (400 ml) at −75°. After stirring 1 h at −75°, the batch was warmed to −10°; H_2O (30 ml) was cautiously added, and then a solution of 98% H_2SO_4 (28 ml) in H_2O (250 ml) was added (stirring and cooling). The aqueous layer was separated, extracted with Et_2O (2 × 100 ml), and discarded. The combined Et_2O extract was washed with 5% NaOH and then brine, dried ($MgSO_4$), and evaporated and the residue was distilled to give 15.1 g (98%) of an alcohol mixture, bp 76–81° (5 mm), that contained ~85% of (−)-3-isothujanol (9) by GLC.

The alcohol mixture (14.9 g, 0.097 mol) was treated, in pyridine, with *p*-nitrobenzoyl chloride (25.0 g, 0.135 mol) and worked up as previously described[15] to give a yellow solid (32.0 g) which after three recrystallizations from MeOH gave 16.5 g (56%) of pure **(−)-3-isothujanol *p*-nitrobenzoate (14)**: mp 88–89°; $[\alpha]^{23}D$ −12.2° (*c* 1.05, $CHCl_3$) [lit.[15] mp 90°; $[\alpha]^{18}D$ −12.5° (*c* 1.0, $CHCl_3$)]. The ester (16.3 g, 0.054 mol) was refluxed for 3 h with KOH (5.6 g, 0.1 mol) in MeOH (150 ml). The solution was cooled, filtered, and evaporated and H_2O (50 ml) was added to the residue. The oil that separated was extracted with Et_2O (3 × 75 ml), the Et_2O extract was washed with H_2O and then brine, dried, and evaporated, and the residue was distilled to give 8.0 g (97%) of chromatographically pure (GLC, TLC) 9: mp 27–28°; bp 76–78° (5 mm); $[\alpha]^{23}D$ −9.4° (*c* 1.92, 95% EtOH) [lit.[15] mp 22–23°; bp 96° (13 mm); $[\alpha]^{20}D$ −8.84° (*c* 1.3, 95% EtOH)].

(−)-3-Isothujanol *p*-Toluenesulfonate (10). A solution of 9 (6.3 g, 40.9 mmol) in dry pyridine (100 ml) was treated at 0° with *p*-toluenesulfonyl chloride (15.2 g, 80 mmol). After 12 h at

0–5° and an additional 60 h at 25° standard workup gave a syrup which was crystallized from MeOH (cooling to −75°) to give 10.7 g (85%) of **10**: mp 57–58°. One recrystallization from MeOH of material from a similar preparation gave pure material: mp 57–58°; $[\alpha]^{23}D$ −9.7° (*c* 1.07, 95% EtOH). Anal. ($C_{17}H_{24}SO_3$) C, H.

(±)-3-Isothujanol *p*-Nitrobenzoate (15). The tosylate from above (10.7 g, 0.035 mol), Ac_2O (1.0 g), anhydrous NaOAc (4.5 g, 0.054 mol), and AcOH (450 ml) were kept for 20 h at 50°. AcOH was evaporated in vacuo, H_2O (30 ml) was added to the residue, and the aqueous solution was extracted with Et_2O (2 × 50 ml). The Et_2O extract was washed with excess 5% $NaHCO_3$ and then brine, dried ($MgSO_4$), and evaporated to give crude **12** (5.9 g) which was dissolved in Et_2O (50 ml) and added dropwise to a solution of $LiAlH_4$ (1.3 g, 0.034 mmol) in Et_2O (200 ml). After 2 h at reflux, the mixture was worked up as described for crude **9** to give the crude (±)-alcohol (4.62 g, 86%) which was treated with *p*-nitrobenzoyl chloride (12.0 g, 0.065 mol) in dry pyridine at 25–30°. After keeping overnight, the mixture was worked up as described[15] and the crude product recrystallized twice from MeOH to give **15** (6.4 g, 61%): mp 72–74°; $[\alpha]^{23}D$ 0.0° (*c* 1.83, $CHCl_3$). Anal. ($C_{17}H_{21}NO_4$) C, H, N.

(±)-3-Isothujanol (13). The (±) ester **15** was hydrolyzed and worked up a described for the hydrolysis of 14 to **9** to give pure **13** (88%): bp 76–78° (5 mm); $[\alpha]^{23}D$ 0.0°. This material was chromatographically (GLC, TLC) and spectroscopically identical (except for optical rotation) with **9** above.

(±)-3-Isothujone (6). Brown[19] oxidation of (±)-3-isothujanol (3.27 g, 0.021 mol) from above followed by chromatography as described for **2** above gave pure **6** (2.7 g, 84%), bp 83–84° (20 mm), $[\alpha]^{23}D$ 0.0° (neat), which was identical (GLC, TLC, spectroscopically), except for optical rotation, with pure **2** described above. The racemic ketone was further characterized as its 2,4-dinitrophenylhydrazone **19** that showed mp 102–103.5° (2-PrOH). Anal. ($C_{16}H_{20}N_4O_4$) C, H, N.

Acknowledgment. We wish to thank Dr. D. M. Cartlidge (MacMillan Bloedel Research Ltd., Vancouver, British Columbia, Canada) for a generous gift of Western Red Cedar leaf oil and Mr. Robert Eiserle (Fritsche, Dodge, and Olcott, Inc., New York, N.Y.) for a generous sample of purified Dalmatian Sage oil. The authors are indebted to Mrs. Louise Atwell for the analgesic testing and to Mr. William Landis and Mr. Noel Whittaker for mass spectral determinations.

References and Notes

(1) D. V. Banthorpe, D. Baxendale, C. Gatford, and S. R. Williams, *Planta Med.*, **20**, 147 (1971).
(2) E. Guenther in "The Essential Oils", Vol. 5, Van Nostrand, New York, N.Y., 1952, p 487.
(3) J. del Castillo, M. Anderson, and G. M. Rubottom, *Nature (London)*, **253**, 365 (1975).
(4) Considerable confusion has resulted from the use of two systems of nomenclature for the 3-thujones and 3-thujanols. Thus it is not clear whether the 3-thujone discussed by del Castillo et al.[3] was meant to represent (+)-3-thujone (**1**), (−)-3-isothujone (**2**), or a mixture of these, since neither the sign of optical rotation, the stereochemical structure of the keto form, nor the system of nomenclature was specified. The uniform system of nomenclature for these compounds proposed by Brown[25] and adopted by others[14,18] has been used by us throughout this paper.
(5) R. S. Wilson and E. L. May, *J. Med. Chem.*, **18**, 700 (1975).
(6) (a) R. S. Wilson and E. L. May, Abstracts, 168th National Meeting of the American Chemical Society, Atlantic City, N.J., Sept 1974, MEDI 11; (b) R. S. Wilson and E. L. May, unpublished result.
(7) M. S. Bergqvist and T. Norin, *Ark. Kemi*, **22**, 137 (1964).
(8) T. Norin, *Acta Chem. Scand.*, **16**, 640 (1962).
(9) E. H. Massey, H. E. Smith, and A. W. Gorden, *J. Org. Chem.*, **31**, 684 (1966).
(10) H. E. Smith, J. C. D. Brand, E. H. Massey, and L. J. Durham, *J. Org. Chem.*, **31**, 690 (1966).
(11) G. Ohloff, G. Uhde, A. F. Thomas, and E. sz. Kovàts, *Tetrahedron*, **22**, 309 (1966).
(12) M. R. Cox, H. P. Koch, W. B. Whalley, M. B. Hursthouse, and D. Rogers, *Chem. Commun.*, 212 (1967).
(13) R. Mechoulam and Y. Gaoni, *Tetrahedron Lett.*, 1109 (1967).
(14) V. Hach, R. W. Lockhart, E. C. McDonald, and D. M. Cartlidge, *Can. J. Chem.*, **49**, 1762 (1970).
(15) A. G. Short and J. Read, *J. Chem. Soc.*, 2016 (1938).
(16) D. V. Banthorpe and H. S. Davies, *J. Chem. Soc. B*, 1356 (1968).
(17) M. I. Goryaev and Z. K. Gemaddenov, *Zh. Prikl. Khim. (Leningrad)*, **38**, 213 (1965).
(18) V. Hach, *J. Org. Chem.*, **38**, 293 (1973).
(19) H. C. Brown, C. P. Gary, and K. T. Liu, *J. Org. Chem.*, **36**, 387 (1971).
(20) T. Norin, *Tetrahedron Lett.*, 37 (1964).
(21) (a) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, **107**, 385 (1953); (b) A. E. Jacobson and E. L. May, *J. Med. Chem.*, **8**, 563 (1965).
(22) T. D. Perrine, L. Atwell, I. B. Tice, A. E. Jacobson, and E. L. May, *J. Pharm. Sci.*, **61**, 86 (1972).
(23) Emulphor (El-620) is a polyoxyethylated vegetable oil which was purchased from GAF Corp., New York, N.Y.
(24) J. C. Cradock, J. P. Davignon, C. L. Sitterst, and A. M. Guarino, *J. Pharm. Pharmacol.*, **25**, 345 (1973).
(25) S. P. Achrya, H. C. Brown, A. Suzuke, S. Nozawa, and M. Itoh, *J. Org. Chem.*, **34**, 3015 (1969).

Synthesis and Pharmacology of Novel Anxiolytic Agents Derived from 2-[(Dialkylamino)methyl-4*H*-triazol-4-yl]benzophenones and Related Heterocyclic Benzophenones

Martin Gall,* J. B. Hester, Jr., A. D. Rudzik, and R. A. Lahti

The Upjohn Company, CNS Diseases Research, Kalamazoo, Michigan 49001. *Received October 24, 1975*

A series of novel [(dialkylamino)methyl-4*H*-1,2,4-triazol-4-yl]benzophenones and related compounds has been prepared via total synthesis from substituted aminodiphenylmethanes or by hydrolysis and subsequent methylation of triazolobenzodiazepines. These new triazole compounds were found to have potent sedative and muscle relaxing activity in mice (i.e., these compounds depressed the traction and dish reflexes). In addition, the title compunds antagonized the clonic convulsions induced in mice by the administration of pentylenetetrazole (Metrazol, 85 mg/kg), with ED_{50}'s varying from 2.0 to 23.0 mg/kg, and the lethality induced by thiosemicarbazide, with ED_{50}'s varying from 0.02 to 9.0 mg/kg. In several biological tests, the potency of seven new benzophenone derivatives approached or exceeded that of diazepam (**35a**) or its glycylaminobenzophenone analogue **36**.

Two recent but unrelated developments in the benzodiazepine antianxiety–hypnotic area have received considerable attention. First, Hester and co-workers[1a] and others in Japan[1b] demonstrated that the fusion of a triazole