Analogs of cannabinoids: synthesis of some 7*H*-indolo-, 5*H*-imidazolo, 7*H*-benzimidazolo[1,2-*c*] [1,3]benzoxazines – novel ring systems

V. K. MAHESH, MAMTA MAHESWARI, RAKESH SHARMA, AND RASHMI SHARMA

Department of Chemistry, University of Roorkee, Roorkee (U.P.) 247667, India

Received August 13, 1984

V. K. MAHESH, MAMTA MAHESWARI, RAKESH SHARMA, and RASHMI SHARMA. Can. J. Chem. **63**, 632 (1985).

Tetrahydrocannabinol **1**, the active constituent of *Cannabis sativa Linn*, is a well-known CNS-active compound and introduction of a nitrogen atom at the ring junction of the pyran and alicyclic ring is of considerable interest. This prompted the synthesis of 7*H*-indolo[1,2-*c*] [1,3]-, 5*H*-imidazolo[1,2-C] [1,3],- and 7*H*-benzimidazolo[1,2-*c*] [1,3]-benzoxazine, a novel heterocyclic system. 2-(2′-Hydroxyphenyl) indoles, 2-(2′-hydroxyphenyl) imidazoles, and 2-(2′-hydroxyphenyl) benzimidazoles are suitable intermediates for the preparation of this type of benzoxazines, as the second heterocycle (ring B) can then be constructed by introduction of a methylene bridge between the hydroxyl of the 2′-hydroxy phenyl substituent and the imino group of the heterocyclic system.

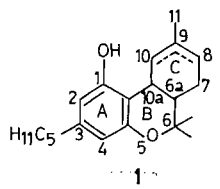
V. K. MAHESH, MAMTA MAHESWARI, RAKESH SHARMA et RASHMI SHARMA. Can. J. Chem. **63**, 632 (1985).

Le tétrahydrocannabinol (**1**), le constituant actif du *Cannabis sativa Linn* est un composé dont l'activité sur le CNS est bien connue et l'introduction d'un atome d'hydrogène à la jonction entre le cycle pyranne et l'alicycle présente beaucoup d'intérêt. Ceci nous a conduit à réaliser la synthèse des 7*H*-indolo[1,2-*c*], 5*H*-imidazolo[1,2-*c*] et 7*H*-benzimidazolo[1,2-*c*] [1,3]benzoxazines, un nouveau système hétérocyclique. Les (hydroxy-2 phényl)-2 indoles, (hydroxy-2 phényl)-2 imidazoles et (hydroxy-2 phényl)-2 benzimidazoles sont des intermédiaires bien adaptés à la préparation de ce type de benzoxazines puisque le deuxième hétérocycle (cycle B) peut alors être construit par l'introduction d'un pont méthylène entre l'hydroxyle du substituant hydroxy-2′ phényle et le groupe imino du système hétérocyclique.

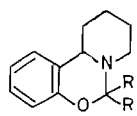
[Traduit par le journal]

Introduction

Tetrahydrocannabinols **1**, active constituents of *Cannabis sativa Linn*, are among a very small number of non-nitrogenous compounds which are central nervous active. To bring about a suitable modification in the activity, several nitrogen-containing analogs have been synthesized; some of these compounds showed CNS activity, but no separation of biological activities could be achieved (1–6). Introduction of a nitrogen atom at the ring junction of the pyran ring (ring B) and the alicyclic ring (ring C) of THC appears to be of considerable interest in studying the structure–activity relationship among this class of compounds. 9,10,11,11a-Tetrahydro 6*H*,8*H*-pyrido[1,2-*c*] [1,3]benzoxazine **2** has been prepared as a model compound containing a nitrogen atom at the ring junction (7).



1

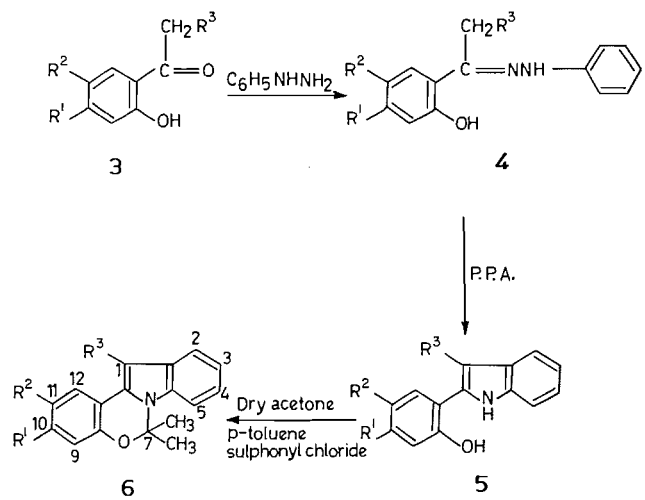


2

Some well-known CNS-active agents are reported to have indole, imidazole, and benzimidazole in their structural makeup (8–10); therefore it was thought that molecules having mixed features of cannabinoids (ring A and B) and substituted pyrrole and imidazole as ring C, with a nitrogen atom as a part of both ring B and C, would be of great pharmacological interest. Such heterocyclic systems would be novel and have not been prepared before. In this paper we wish to report on the preparation and studies of 7,7-dimethyl-7*H*-indolo[1,2-*c*] [1,3]benzoxazines, 5*H*-imidazolo[1,2-*c*] [1,3]benzoxazines, and 7*H*-benzimidazolo[1,2-*c*] [1,3]benzoxazine.

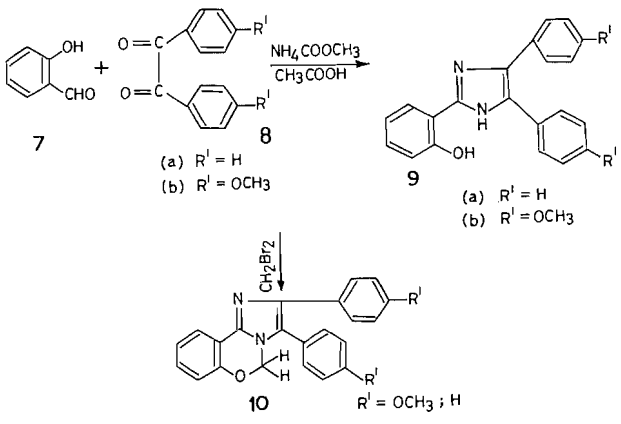
Discussion

For the preparation of the benzoxazine systems an ingenious method has been developed. A methylene bridge has been constructed between the hydroxyl group of the 2′-hydroxy-phenyl substituent and the imino group of the heterocyclic system – indole, imidazolo, or benzimidazole. This is achieved by boiling the properly substituted heterocyclic compound with either (a) dry acetone in presence of *p*-toluene sulphonyl chloride (11) or (b) methylene dibromide in potassium carbonate – dimethylformamide mixture. 2-(2′-Hydroxyphenyl) indoles, on refluxing in dry acetone in presence of *p*-toluene sulphonyl chloride, gave the expected product, 7,7-dimethyl-7*H*-indolo[1,2-*c*] [1,3]benzoxazines, in good yields. The use of methylene dibromide, however, resulted in a number of compounds, from which the expected 7*H*-indolo[1,2-*c*] [1,3]benzoxazine could not be isolated (12). Condensation of 2-(2′hydroxyphenyl) imidazoles and 2-(2′-hydroxyphenyl) benzimidazoles with methylene dibromide in K_2CO_3–DMF gave 5*H*-imidazolo[1,2-*c*] [1,3]benzoxazines and 7*H*-benzimidazolo[1,2-*c*] [1,3]benzoxazines. It has also been noted that the phenolic group in ring A is essential for the biological activity (13, 14).

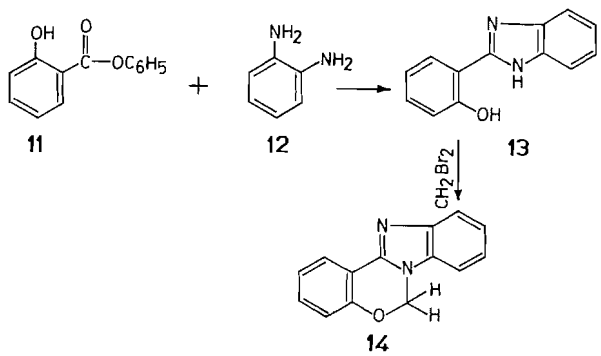


3 4 6 5

SCHEME I



SCHEME 2



SCHEME 3

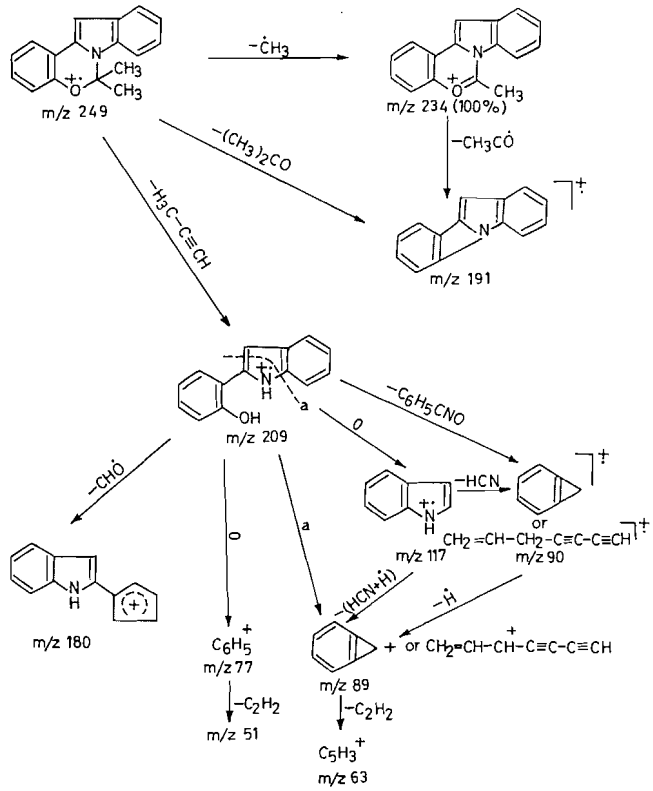


CHART 1

Nuclear magnetic resonance studies

The nmr spectrum of 7,7-dimethyl-7*H*-indolo[1,2-*c*] [1,3]-benzoxazine **6***a* showed a sharp singlet at δ 1.81 for the *gem*-dimethyl at the 7 position. The other protons of benzoxazine are at comparable values to the 2-(2′-hydroxyphenyl indole) protons. In the case of the imidazolo benzoxazines, in addition to the signals for aromatic protons, a singlet at δ 5.67 integrating for two protons which can be assigned to methylene protons at position 5 in the molecule has been observed.

Mass spectral analyses

The molecular ions in the mass spectra of compounds 7,7-dimethyl-7*H*-indolo[1,2-*c*] [1,3]benzoxazine **6***a* and its 10-hydroxy derivative **6***g* appeared at *m/z* 249 to 265 respectively. Loss of one methyl radical from molecular ion **6***a* at position 7 resulted in the predominant fragment at *m/z* 234 which is the base peak. The molecular ions undergo a loss of propyne molecule to yield an ion at *m/z* 209 which corresponds to the molecular weight of the 2-(2′-hydroxyphenyl) indole ion. These ions split into further fragments which are common in 2-phenyl indoles (15), shown in Chart 1. However, a peak at *m/z* 117 which corresponds to unsubstituted indoles definitely results by a rearrangement process. The ion displays all the characteristic fragmentations reported for indoles (16).

The molecular ion of compound **6***a* also suffers a loss of acetone molecule resulting in an ion at *m/z* 191. An alternative pathway to this ion, *m/z* 191, involves the loss of acetyl radical from the peak cation appearing at *m/z* 234 (Chart I). The most intense peaks in the mass spectra of the compound **6***a* are *m/z* 249, 234(100%), 209, 191, 180, 117, 90, 89, 77, 63, and 51. Spectral peaks *m/z* 265, 250(100%), 225, 196, 117, 89, 77, 63, and 51 in the case of the 10-hydroxy derivative can be explained in a similar way.

Experimental

All melting points reported are uncorrected. Infrared spectra were reported on a Beckman IR-20 spectrophotometer (λ_{max} in cm^{-1}) and nmr spectra were recorded on Varian A-60D and Brucker WH-270 spectrometers with TMS as an internal standard. The mass spectra were scanned on a spectrophotometer equipped with a direct inlet system at 70 eV and at filament current 100 μA. Compounds were routinely checked for their homogeneity by tlc on silica gel-G plates and spots were visualized by exposure to iodine vapours.

Corresponding phenylhydrazones were prepared by condensation of phenylhydrazine with respective acetophenones, propiophenones, and butrophenones (17), which in turn were prepared by condensation of phenols or resorcinols with the corresponding carboxylic acids.

*2-(2′-Hydroxyphenyl) indole (**5**)*

A mixture of 2-hydroxyacetophenone phenylhydrazone (8.4 g, 0.04 mol) and polyphosphoric acid (60 g, prepared from 40 g phosphorous pentoxide and 20 g orthophosphoric acid) was heated on an oil bath at 120°C for 1 h and left overnight at room temperature. The reaction mixture was poured into ice-cold water. The precipitated product was filtered, washed with water, and dried. It was crystallized from methanol to yield 5.0 g (68%) of the title compound, mp 162–164°C; ir (KBr): 3445, 3440 (OH and NH) cm^{-1}; nmr (DSS) (NaOD): 6.68 (t, 1, H-3′), 6.82 (m, 1, H-5′), 7.18–7.35 (m, 4, H-3, H-4, H-4′, H-6′), 7.54 (d, J = 6.7 Hz, 1, H-5), 7.65 (d, J = 6.7 Hz, 1, H-6), 7.70 (d, J = 6.7 Hz, 1, H-7).

*7,7-Dimethyl-7H-indolo[1,2-c] [1,3]benzoxazine (**6**a)*

A mixture of 2-(2′-hydroxyphenyl) indole (**5**) (3.0 g, 0.015 mol), *p*-toluene sulphonyl chloride (0.05 g), and dry acetone (50 mL) was refluxed on a steam bath for 50 h. The solvent was removed *in vacuo*. The residue was taken up in chloroform and washed with water, dried (Na_2SO_4), filtered, and concentrated to yield 2 g (56%) of the title compound which, after recrystallization from ethanol/ethyl acetate (1:1), had mp 110–112°C; nmr: ($CDCl_3$): 6.00 (s, 2H, $2CH_3$), 6.88–7.97 (m, 9H, ArH); ms *m/e* (%): 249(55), 234(100), 209(27), 180(19), 117(48), 90(20), 89(26), 77(25), 63(32), 51(28), 191(31).

TABLE 1. Physical data of 7,7-dimethyl-7*H*-indolo[1,2-*c*] [1,3]benzoxazines (**6**)

Compound No.	R^1	R^2	R^3	Yield (%)	Melting point (°C)	Molecular formula	Analysis (%) Calculated	Found
a	H	H	H	60	111	$C_{17}H_{15}NO$	C: 81.92	81.64
							H: 6.02	5.92
							N: 5.62	5.36
b	CH_3	H	H	55	105	$C_{18}H_{17}NO$	C: 82.13	82.00
							H: 6.46	6.35
							N: 5.32	5.20
c	Cl	CH_3	H	65	135	$C_{18}H_{16}ClNO$	C: 72.60	72.50
							H: 5.38	5.25
							N: 4.70	4.44
d	CH_3	H	CH_3	50	Viscous oil	$C_{19}H_{19}NO$	C: 82.31	82.09
							H: 6.86	6.85
							N: 5.05	4.80
e	H	CH_3	H	50	93	$C_{18}H_{17}NO$	C: 82.13	81.92
							H: 6.46	6.32
							N: 5.32	5.27
f	H	OCH_3	H	55	110	$C_{18}N_{17}NO_2$	C: 77.42	77.35
							H: 6.09	5.85
							N: 5.01	4.85
g	OH	H	H	55	173	$C_{17}H_{15}NO_2$	C: 76.98	76.82
							H: 5.66	5.48
							N: 5.28	5.02
h	OH	H	CH_3	48	86	$C_{18}N_{17}NO_2$	C: 77.42	77.38
							H: 6.09	5.75
							N: 5.01	4.86
i	OH	H	C_2H_5	53	72	$C_{19}H_{19}NO_2$	C: 77.81	77.60
							H: 6.48	6.32
							N: 4.78	4.56
j	H	CH_3	CH_3	56	115	$C_{19}H_{19}NO$	C: 82.31	82.20
							H: 6.86	6.80
							N: 5.03	4.85
k	OH	C_2H_5	H	50	144	$C_{19}H_{19}NO_2$	C: 77.81	77.80
							H: 6.48	6.30
							N: 4.78	4.75
l	H	H	CH_3	46	50	$C_{18}H_{17}NO$	C: 82.13	82.00
							H: 6.46	6.35
							N: 5.32	5.25

*11-Methoxy-7,7-dimethyl-7*H*-indolo[1,2-c] [1,3]benzoxazine (**6**b)*

Condensation of 2(2′-hydroxy-5-methoxyphenyl) indole (2.4 g, 0.01 mol) in a similar way with dry acetone and *p*-toluene sulphonyl chloride yielded the 11-methoxy derivative (**6***b*). It was crystallized from ethanol/ethyl acetate (1:1) to give 1.28 g (55%) of the title compound, mp 110–111°C; nmr ($CDCl_3$): 1:818 (6H, $(CH_3)_2$), 2:22 (s, 3H, CH_3), 6.81–7.59 (m, 8H, ArH).

*10-Hydroxy-7,7-dimethyl-7*H*-indolo[1,2-c] [1,3]benzoxazine (**6**g)*

By the same procedure used for the preparation of **6***a*, 2-(2′,4′-dihydroxyphenyl) indole (2.25 g, 0.01 mol) was converted to 1.3 g (55%) of the title compound, mp 170–173°C; nmr ($CDCl_3$ + DMSO-d_6): 1.75 (s, 6H, $(CH_3)_2$), 4.83 (m, 1H, OH), 6.83–7.71 (m, 8H, ArH).

*2-(2′-Hydroxyphenyl)-4,5-diphenyl imidazole (**9**a)*

A mixture of salicylaldehyde (6.1 g, 0.05 mol), benzil (10.5 g, 0.05 mol), ammonium acetate (30 g), and glacial acetic acid (150 mL) was refluxed for a period of 2 h, cooled, and treated with ice-cold water to give 10 g (64%) of the title compound which, after recrystallization from methanol/ether, had mp 238–240°C; ir(KBr): 3435, 3250 (OH and NH) cm^{-1}. *Anal.* calcd. for $C_{21}H_{16}N_2O$: C 80.76, H 5.13, N 8.9; found: C 80.45, H 5.00, N 8.87.

*2,3-Diphenyl-5*H*-imidazolo[1,2-c] [1,3]benzoxazine (**10**)*

A mixture of 2-(2′-hydroxyphenyl)-4,5-diphenyl imidazole (**9***a*) (3.12 g, 0.01 mol), anhydrous potassium carbonate (10 g), methylene bromide (7 mL), and dry dimethylformamide (40 mL) was heated on a steam bath for 16 h. It was filtered to remove the inorganic salts and the filtrate was concentrated under vacuum. The residue was triturated with water to yield 2.4 g (74%) of the title compound, mp 60–62°C; nmr ($CDCl_3$): 7.60–7.03 (m, 14, ArH), 1.67 (s, 2, H-5).

*2-(2′-Hydroxyphenyl)-4,5-bis(*p*-methoxyphenyl) imidazole (**9**b, R′ = OCH_3)*

This compound was prepared in a similar way as **9** from 4,4′-dimethoxy benzil (**8***b*) (2.7 g, 0.01 mol) and salicylaldehyde (**7**) (1.22 g, 0.01 mol) to yield 2.38 g (70%) of the title compound, mp 92–95°C; nmr (TFA): 3.90 (s, 6, $(OCH_3)_2$, 6.65–7.45 (m, 12, ArH), 3.16 sweep of set 500 Hz (m, 2, NH, OH). *Anal.* calcd. for $C_{23}H_{20}N_2O$: N 8.23; found: N 8.00.

*2,3-Bis(*p*-methoxyphenyl)-5*H*-imidazolo[1,2-c] [1,3]benzoxazine (**10**, R′ = OCH_3)*

This compound was prepared by condensation of 2-(2′-hydroxyphenyl)-4,5-bis(*p*-methoxyphenyl) imidazole (**9***b*) (1.7 g, 0.005 mol) with methylene bromide, as in the method described above for **9***a* (R′ = H) to yield 1.23 g (70%) of the title compound, mp 80°C; nmr($CDCl_3$): 3.97 (s, 6, $(OCH_3)_2$), 5.80 (s, 2, H-5), 7.10–8.30 (m, 12, ArH). *Anal.* calcd. for $C_{24}H_{20}N_2O$: C 81.82, H 5.68, N 7.95; found: C 81.65, H 5.50, N 7.72.

*2-(2′-Hydroxyphenyl) benzimidazole (**13**)*

A mixture of phenyl salicylate (8.56 g, 0.04 mol) and *O*-

phenylenediamine (4.32 g, 0.04 mol) was heated at 180°C in an oil bath for 5 h; the reaction mixture was cooled and then dissolved in 10% sodium hydroxide solution. It was acidified with ice-cold acetic acid to give 6.0 g (71%) of the title compound, mp 240–241°C (lit. (18) mp 238°C); ir(KBr): 3430, 3320 (OH and NH) cm^{-1}.

*7H-Benzimidazolo[1,2-c] [1,3]benzoxazine (**14**)*

To a solution of 2-(2′-hydroxyphenyl) benzimidazole (4.2 g, 0.02 mol) in dry dimethylformamide (40 mL) in the presence of anhydrous potassium carbonate (5 g), methylene bromide (7 mL) was added and the reaction mixture was filtered and concentrated under vacuum. The residue was treated with chilled water to yield 3.1 g (70%) of the title compound, mp 151–153°C; nmr ($CDCl_3$): 6.00 (s, 2H, $—CH_2$), 7.10–8.17 (m, 8H, ArH); *m/e* (%) ms: 222(100), 221(100), 220(10), 194(83), 193(100), 169(53), 168(100), 167(67), 140(34), 113(100), 104(41), 103(50), 98(71), 93(35), 91(34), 85(41), 79(100).

Acknowledgement

One of the authors (R.S.) thanks the C.S.I.R., New Delhi for financial assistance.

1. R. M. ANKER and A. H. COOK. J. Chem. Soc. 58 (1946).
2. H. G. PARS, F. E. GANEHELLI, J. K. KELLER, and R. K. RAZADAN. J. Am. Chem. Soc. **88**, 3664 (1966).
3. H. G. PARS and R. K. RAZDAN. Ann. N.Y. Acad. Sci. **191**, 15 (1971).
4. W. L. DEWEY, L. S. HARRIS, J. F. HOWES, J. S. KENNEDY, F. E. CARANEHELLI, H. G. PARS, and R. K. RAZDAN. Nature (London) **226**, 1267 (1970).
5. M. CUSHMAN and N. CASTAGNOLLI, JR. J. Org. Chem. **38**, 440 (1973).
6. M. CUSHMAN and N. CASTAGNOLLI, JR. J. Org. Chem. **39**, 1546 (1974).
7. O. P. MALIK, R. S. KAPIL, and N. ANANAND. Indian J. Chem. **14B**, 975 (1976).
8. M. N. RAPPORT. J. Biol. Chem. **180**, 961 (1949).
9. P. MILLEE, J. P. MALRIAN, J. BENIAM, J. Y. LALLEMAND, and M. JULIA. J. Med. Chem. **11**, 207 (1968).
10. H. H. PENNES and P. H. HOCK. Am. J. Psychiat. **113**, 887 (1957).
11. A. W. D. AVISOR, A. L. MORRISON, and M. W. PARKES. J. Chem. Soc. 952 (1949).
12. E. C. TAYLOR, K. LENARD, and B. LOEV. Tetrahedron, **23**, 77 (1967).
13. A. CALVAIRE and R. PALLOUD. C. R. Acad. Sci. **250**, 3194 (1960).
14. V. K. MAHESH, M. MAHESHWARI, and R. SHARMA. Chem. Ind. 200 (1980).
15. J. C. POWERS. J. Org. Chem. **33**, 2044 (1968).
16. Catalog of Mass Spectra Data, American Petroleum Institute Research Project 44, Carnegie Institute of Technology, Pittsburgh Pa. Spectra No. 623.
17. C. M. BREWESTER and J. C. HARRIS. J. Am. Chem. Soc. **52**, 4869 (1930).
18. I. S. IOFFE and D. N. GLEBOVSKII. Zh. Obshch. Khim. **30**, 1158 (1960).