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Synthesis and Carcinogenic Activity of Oxidized Benzacridines: Potential Metabolites of the Strong Carcinogen 7-Methylbenz[c]acridine and of the Inactive Isomer 12-Methylbenz[a]acridine

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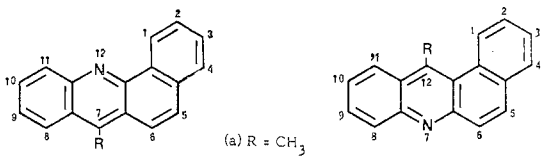
The synthesis of 15 compounds related either to the benz[c]acridine or to the benz[a]acridine series is reported. Spectral data, i.e., NMR and EI fragmentation, are given. These compounds were tested for carcinogenic activity in mice of the XVIInc/Z strain by subcutaneous injection. Only three weak carcinogens were detected, 5,6-dihydro-5,6-dihydroxy-12-methylbenz[a]acridine, 3-methoxy-7-methylbenz[c]acridine, and 4-acetoxy-7-methylbenz[c]acridine. These results are discussed with consideration to the data previously obtained with other benzacridines and condensed quinolines.

Aza arenes are common pollutants in urban and industrial atmospheres and are of increasing concern, since they are present in liquid and gaseous fuels derived from coal and shale oil.[1-5] In the present context of depletion of conventional resources of energy, the industrial production of synthetic fuels is strongly required; however, it may become a potential health hazard for man, since they may contain aza heterocycles, among which many were found carcinogenic in animal experiments.[6,7]

For the last 35 years our team has widely investigated the chemistry and biological activity of numerous compounds related to the benzacridine family. However, in spite of the tremendous proliferation of studies devoted to the metabolic activation and the biochemical reactions of carcinogenic polycyclic hydrocarbons (PAH), nitrogen analogues of PAH have not been yet extensively studied.

Nevertheless, recent reports did show some interest in that field within the arene oxide pathway of metabolic activation at the K region[8] or at the bay region.[9] Physicochemical and theoretical studies gave some controversial results in agreement either with the K region theory[10-13]



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or with the Jerina's bay region theory,[14] and, in spite of recent communications related to the synthesis of possible metabolites of benzacridine derivatives[15-20] and to the overall estimation of 7-methylbenz[c]acridine (**1a**) metabolism,[21] the situation remains unclear.

As reported earlier, most carcinogens of the benzacridine family belong to the benz[c]acridine series, whereas very few compounds of the benz[a]acridine series show such an adverse property.[6] The most typical example is actually 7-methylbenz[c]acridine (**1a**) and 12-methylbenz[a]acridine (**2a**), which were very thoroughly investigated in our laboratory for carcinogenicity with various strains of mice and various modes of application. 7-Methylbenz[c]acridine (**1a**) is a very potent carcinogen (100% tumor incidence in 26 experiments), whereas **2a** is totally inactive (0% tumor incidence in 24 experiments).[6,22]

In the present paper we report the synthesis and the carcinogenic activity of a series of oxidized derivatives of **1** and **2**.

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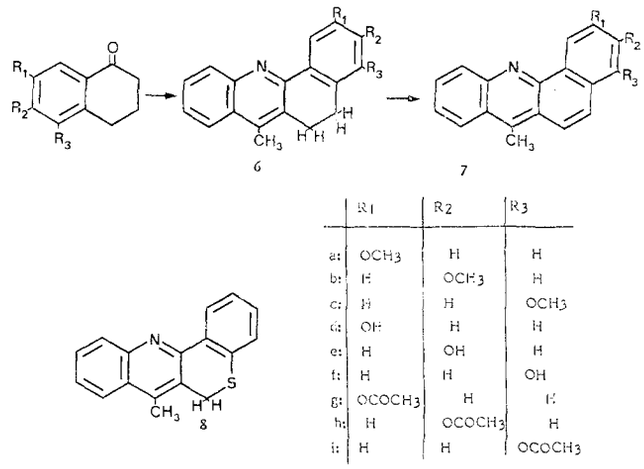
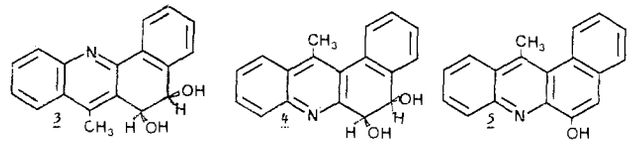
Scheme I



The reaction of osmium tetroxide with methylbenzacridines has been studied in the benz[c]acridine series,[23] and **1a** has been successfully converted to *cis*-5,6-dihydro-5,6-dihydroxy-7-methylbenz[c]acridine (**3**).[17] In the present study, *cis*-5,6-dihydro-5,6-dihydroxy-12-methylbenz[a]acridine (**4**) was also obtained and characterized as a very unstable compound, leading readily to 6-hydroxy-12-methylbenz[a]acridine (**5**). In contrast, diol **3** failed to undergo dehydration to a phenol.



The very easy transformation of diol **4** to phenol **5** results probably from an intramolecular interaction of the hydroxy group at carbon 6 with the nitrogen atom, as shown by the strong downfield shift of the corresponding signal in the ^1H NMR spectrum of 4.

Finally, the Friedlaender–Kempter synthesis of quinolines[24] applied to 5-, 6-, and 7-methoxy-1-tetralone led to the 5,6-dihydro derivatives of 2-, 3-, and 4-methoxy-7-methylbenz[c]acridine (**6a–c**), respectively, which underwent easy dehydrogenation to **7a–c**. These last compounds were readily demethylated to the corresponding phenols **7d–f** by means of pyridinium chloride and subsequently converted to the acetoxy derivatives **7g–i** (Scheme I).

^1H NMR spectra of non-K derivatives have been recorded at 60 MHz and empirically interpreted, whereas compounds **3–5** have been examined at 100 MHz, assignments being made using standard decoupling methods (Indor and double resonance).

Results and Discussion

As previously observed with polycyclic hydrocarbons, oxidized compounds show generally a lower carcinogenic potency than the parent molecules.[26,27] This is particularly true for the benz[c]acridine series for which only **7b** and **7i** were shwon weakly carcinogenic (1/21 and 1/28 sarcomas at the injection site, respectively). Interestingly, these two compounds still bear a free 1–2 bond (bay region). This observation is consistent with a previous one related to the fluoro derivatives of 6*H*-[1]benzothiopyrano[4,3-*b*]quinoline (**8**) whose sarcomagenic properties are considerably enhanced upon substitution of the 4-position by a fluorine atom, whereas substitution at the 2- or 3-position completely suppresses the activity.[28]

On the other hand, the positive results obtained with 5,6-dihydro-5,6-dihydroxy-12-methylbenz[a]acridine (**4**) (2 animals with tumors among 28 treated) were actually unexpected on the basis of our present knowledge of the carcinogenic activity generally observed with benz[c]acridine derivatives and the lack of such properties for the members of the benz[a]acridine family.[6]

The accessibility of the nitrogen atom in the last series may account for this difference, and the probable interaction between the nitrogen and the OH group at carbon 6 of the diol (or of the phenol resulting from in vivo dehydration) might sterically block the nitrogen's accessibility; unfortunately, we were unable, for practical reasons, to test phenol **5**. However, such an interpretation fails to account for the results obtained with bromomethyl derivatives of both benzacridines **1b** and **2b**, which also show an inversion of the sarcomagenic potency, **2b** being active, whereas **1b** is not.[29] On the other hand, in a recent investigation with the Ames test on *Salmonella*, both **1a** and **2a** were found mutagenic.[22]

Our observations confirm previous ones that were interpreted assuming that the metabolic activation of compounds of the benzacridine family should follow the same processes as those of polycyclic aromatic hydrocarbons.[14,21] However, the simple oxidation products investigated in the present paper give rise to interesting questions in regard to the modulation of carcinogenic activity and clearly show the important role of the nitrogen atom, especially in the benz[a]acridine series. This role still remains unclear. Molecular orbital calculations did not show any dramatic variation, in terms of π electron delocalization, between such a heterocyclic nitrogen system and the analogous hydrocarbon, benz[a]anthracene.[6,14] The nucleophilic character of the nitrogen atom, as well as its steric accessibility, might account for the difference of activity observed between the benz[a]acridine and the benz[c]acridine series. However, only a careful examination of in vitro and in vivo metabolism and of the biochemical interactions at the cell level, presently in progress in our laboratory and in others, will allow further interpretation.

Experimental Section

Chemistry. All melting points are uncorrected. NMR spectra were obtained with a Varian EM 360 (60 MHz, δ in parts per million downfield from Me_4Si) or a Varian XL-100 (100 MHz, δ in parts per million downfield from $CHCl_3$ = 7.25) spectrometer. Mass spectra were recorded on a AEI MS50 at 70 eV by the direct introduction method (probe temperature 150–180 °C). All analyses (CNRS, France) were within 0.3% of the calculated values.

Osmium Tetroxide Oxidation. *cis*-5,6-Dihydro-5,6-dihydroxy-7-methylbenz[*c*]acridine (3). 7-Methylbenz[c]acridine (**1a**; 2×10^{-3} mol) was reacted with osmium tetroxide

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(1.5×10^{-3} mol) for 4 days according to the general procedure described by Cook and Schoental[30] to afford the product in 72% yield: colorless needles (ethyl) acetate); mp 263 °C (lit.[17] mp 248–249 °C); MS, m/z 277 (93.5), 276 (35.5), 260 (21.5), 259 (58.5), 258 (15.5), 249 (23), 248 (100), 243 (37.5), 231 (23), 230 (37.5); NMR (100 MHz; $CDCl_3$) δ 1.78 (d, 1 H exchangeable with D_2O, $J_{6\text{-}H,6\text{-}OH}$ = 8 Hz), 2.76 (d, 1 H exchangeable with D_2O, 5-OH, $J_{5\text{-}H,5\text{-}OH}$ = 10 Hz), 2.85 (s, 3 H, CH_3), 5.04 (q, 1 H, H_5, $J_{5,6}$ = 4 Hz), 5.34 (q, 1 H, H_6), 6.90 (m, 2 H, $H_{2,3}$), 7.10 (m, 2 H, $H_{9,10}$), 7.22 (m, 1 H, H_4), 7.49 (m, 1 H, H_8), 7.56 (m, 1 H, H_{11}), 7.95 (m, 1 H, H_1). Anal. ($C_{18}H_{15}NO_2$) C, H, N. This diol was found highly stable. Attempts to convert it into 5- and/or 6-hydroxy-7-methylbenz[c]acridine either by thermal or acidic dehydration (even with concentrated sulfuric acid) were unsuccessful.

***cis*-5,6-Dihydro-5,6-dihydroxy-12-methylbenz[*a*]acridine (4).** Reaction of osmium tetroxide with **2a** was carried out by the general procedure described by Baran.[31] 12-Methylbenz[a]acridine (**2a**; 2×10^{-3} mol) and OsO_4 (1.5×10^{-3} mol) were dissolved in dry pyridine (20 mL) and kept under nitrogen for 6 days. To this mixture was added with stirring a solution of 1 g of sodium bisulfite, 15 mL of water, and 10 mL of pyridine, and the resulting mixture was allowed to stand overnight. The orange suspension was collected by filtration and extracted 3 times with ethyl acetate (3 × 30 mL). The combined extracts were dried over $MgSO_4$ and evaporated to dryness in vacuo at room temperature. Rapid purification of the residue over SiO_2 (2 × 10 cm) ($CHCl_3$) afforded 4 in 30% yield: slightly colored microprisms; mp 165 °C (decomposition above 145 °C by progressive heating); MS, m/z 277 (3.5), 259 (23.5), 248 (51), 231 (29.5), 230 (100); NMR (100 MHz; $CDCl_3$) δ 2.45 (broad signal, 1 H exchangeable with D_2O, 5-OH), 2.97 (s, 3 H, CH_3), 4.8 (d, 1 H, H_5, $J_{5,6}$ = 3.3 Hz), 4.96 (d, 1 H, H_6), 5.6 (broad signal, 1 H exchangeable with D_2O, 6-OH), 7.69 (m, 1 H, H_{11}), 7.76 (m, 1 H, H_4), 8.08 (m, 1 H, H_1), 8.16 (m, 1 H, H_8), 7.30–7.65 (envelope, 4 H, $H_{2,3,9,10}$). Anal. ($C_{18}H_{15}NO_2$) C, H, N.

Attempts to purify this compound further, as well as heating it in acetic acid solution, led almost quantitatively to **6-hydroxy-12-methylbenz[*a*]acridine (5)**, which crystallized as yellow needles from ethyl alcohol: mp 149 °C; MS, m/z 259 (75.5), 231 (100), 230 (55), 229 (11.5), 228 (18), 216 (19), 202 (18); NMR (100 MHz; $CDCl_3$): 3.4 (s, 3 H, CH_3), 7.28 (s, 1 H, H_5), 7.57 (m, 2 H, $H_{2,3}$), 7.76 (m, 2 H, $H_{9,10}$), 7.88 (m, 1 H, H_{11}), 8.30 (m, 1 H, H_8), 8.39 (m, 1 H, H_4), 8.58 (m, 1 H, H_1), 9.08 (broad signal, 1 H exchangeable with D_2O, OH). Anal. ($C_{18}H_{13}NO$) C, H, N.

Compounds 6a–c and 7a–i. General Procedure. A mixture of 7.5×10^{-3} mol of 5-, 6-, or 7-methoxy-1-tetralone and 5×10^{-3} mol of 2-aminoacetophenone hydrochloride was heated at 140 °C for 10 min. After the mixture was cooled, the residual material was extracted with acetone and treated with dilute ammonium hydroxide. The resulting suspension was then extracted with chloroform, and the organic layer was dried over potassium carbonate and evaporated in vacuo. The residue was purified by crystallization either from cyclohexane or methyl alcohol to afford **6a–c**.

2-Methoxy-7-methyl-5,6-dihydrobenz[*c*]acridine (6a): colorless prisms (CH_3OH); mp 99 °C; yield 87%; NMR (60 MHz; $CDCl_3$) δ 2.6 (s, 3 H, CH_3), 2.93 (m, 4 H, CH_2CH_2), 3.9 (s, 3 H, OCH_3), 6.82 (m, 1 H, H_3), 7.1 (m, 1 H, H_4), 8.12 (m, 2 H, $H_{9,10}$), 8.56 (m, 3 H, $H_{1,8,11}$). Anal. ($C_{19}H_{17}NO$) C, H, N.

3-Methoxy-7-methyl-5,6-dihydrobenz[*c*]acridine (6b): colorless prisms (C_6H_{12}); mp 118 °C; yield 91%; NMR (60 MHz; $CDCl_3$) δ 2.63 (s, 3 H, CH_3), 3.03 (m, 4 H, CH_2CH_2), 3.87 (s, 3 H, OCH_3), 6.8 (m, 1 H, H_4), 6.97 (m, 1 H, H_2), 8.06 (m, 2 H, $H_{8,11}$), 8.54 (m, 1 H, H_1), 7.23–7.83 (envelope, 2 H, $H_{9,10}$). Anal. ($C_{19}H_{17}NO$) C, H, N.

4-Methoxy-7-methyl-5,6-dihydrobenz[*c*]acridine (6c): colorless crystals (CH_3OH); mp 130 °C; yield 84%; NMR (60 MHz; $CDCl_3$) δ 2.6 (s, 3 H, CH_3), 3 (m, 4 H, CH_2CH_2), 3.83 (s, 3 H, OCH_3), 6.83 (m, 1 H, H_3), 7.23 (m, 1 H, H_2), 7.47 (m, 2 H, $H_{9,10}$), 7.93 (m, 2 H, $H_{8,11}$), 8.13 (m, 1 H, H_1). Anal. ($C_{19}H_{17}NO$) C, H, N.

Compounds **6a–c** were subsequently dehydrogenated to the corresponding **methoxy-7-methylbenz[*c*]acridines 7a–c** by distillation over 5% palladium on charcoal. Purification of the methoxyacridines was carried out by chromatography on SiO_2 (benzene–cyclohexane, 1:1) and crystallization.

2-Methoxy-7-methylbenz[*c*]acridine (7a): pale yellow needles (CH_3OH); mp 124 °C; yield 78%; NMR (60 MHz; $CDCl_3$) δ 3.03 (s, 3 H, CH_3), 4.06 (s, 3 H, OCH_3), 7.2 (m, 1 H, H_3), 8.27 (m, 2 H, $H_{8,11}$), 8.93 (m, 1 H, H_1), 7.42–7.9 (envelope, 5 H, $H_{4,5,6,9,10}$). Anal. ($C_{19}H_{15}NO$) C, H, N.

3-Methoxy-7-methylbenz[*c*]acridine (7b): pale yellow needles (C_6H_{12}); mp 139 °C; yield 83%; NMR (60 MHz; $CDCl_3$) δ 3.08 (s, 3 H, CH_3), 4.02 (s, 3 H, OCH_3), 7.66 (d, 1 H, H_5, $J_{5,6}$ = 8 Hz), 8.07 (d, 1 H, H_6), 8.36 (m, 2 H, $H_{8,11}$), 9.5 (m, 1 H, H_1), 7.23–8.03 (envelope, 4 H, $H_{2,4,9,10}$). Anal. ($C_{19}H_{15}NO$) C, H, N.

4-Methoxy-7-methylbenz[*c*]acridine (7c): yellow prisms (C_6H_{12}); mp 203 °C; yield 71%; NMR (60 MHz; $CDCl_3$) δ 3 (s, 3 H, CH_3), 3.97 (s, 3 H, OCH_3), 7 (m, 1 H, H_3), 7.5 (d, 1 H, H_5, $J_{5,6}$ = 8.5 Hz), 7.67 (m, 3 H, $H_{2,9,10}$), 7.98 (d, 1 H, H_6), 8.17 (m, 2 H, $H_{8,11}$), 8.88 (m, 1 H, H_1). Anal. ($C_{19}H_{15}NO$) C, H, N.

Compounds **7a–c** were refluxed in a tenfold excess of pyridinium chloride for 15 min. The resulting solutions were diluted with water (100 mL), and the precipitates were collected and either purified by crystallization to afford **hydroxy-7-methylbenz[*c*]acridine 7d–f** or dissolved in 5% aqueous NaOH. The basic solutions were cooled in an ice bath and treated with a twofold excess of acetic anhydride to form **acetoxy-7-methylbenz[*c*]acridines 7g–i**, which were collected by filtration and purified by chromatography on SiO_2 (benzene).

2-Hydroxy-7-methylbenz[*c*]acridine (7d): yellow needles (toluene); mp 240 °C; yield 69%; NMR (60 MHz; Me_2SO-d_6) δ 3.08 (s, 3 H, CH_3), 7.22 (m, 1 H, H_3), 8.28 (m, 2 H, $H_{8,11}$), 8.7 (m, 1 H, H_1), 9.85 (s, 1 H exchangeable with D_2O, OH), 7.45–8.06 (envelope, 5 H, $H_{4,5,6,9,10}$). Anal. ($C_{18}H_{13}NO$) C, H, N.

3-Hydroxy-7-methylbenz[*c*]acridine (7e): yellow prisms (toluene); mp 263 °C; yield 79%; NMR (60 MHz; $CDCl_3$ + Me_2SO-d_6) δ 3.03 (s, 3 H, CH_3), 7.27 (m, 2 H, $H_{2,4}$), 7.53 (d, 1 H, H_5, $J_{5,6}$ = 8.5 Hz), 7.62 (m, 2 H, $H_{9,10}$), 7.94 (d, 1 H, H_6), (m, 2 H, $H_{8,11}$), 9.2 (m, 1 H, H_1), 9.67 (s, 1 H exchangeable with D_2O, OH). Anal. ($C_{18}H_{13}NO$) C, H, N.

4-Hydroxy-7-methylbenz[*c*]acridine (7f): yellow needles (benzene); mp 254 °C; yield 81%; NMR (60 MHz; $CDCl_3$ + Me_2SO-d_6) δ 3.07 (s, 3 H, CH_3), 7.12 (m, 1 H, H_3), 7.47 (m, 1 H, H_2), 7.67 (m, 2 H, $H_{9,10}$), 7.9 (d, 1 H, H_5, $J_{5,6}$ = 8.5 Hz), 8.12 (d, 1 H, H_6), 8.2 (m, 2 H, $H_{8,11}$), 8.87 (m, 1 H, H_1), 9.7 (s, 1 H exchangeable with D_2O, OH). Anal. ($C_{18}H_{13}NO$) C, H, N.

2-Acetoxy-7-methylbenz[*c*]acridine (7g): yellow microprisms (C_6H_{12}); mp 154 °C; yield 89%: NMR (60 MHz; $CDCl_3$) δ 2.38 (s, 3 H, $COCH_3$), 3 (s, 3 H, CH_3), 7.38 (m, 1 H, H_3), 8.2 (m, 2 H, $H_{8,11}$), 9.13 (d, 1 H, H_1, $J_{1,3}$ = 3 Hz), 7.47–8.03 (envelope, 5 H, $H_{4,5,6,9,10}$). Anal. ($C_{20}H_{15}NO_2$) C, H, N.

3-Acetoxy-7-methylbenz[*c*]acridine (7h): light yellow needles (benzene); mp 171 °C; yield 93%; NMR (60 MHz; $CDCl_3$) δ 2.33 (s, 3 H, $COCH_3$), 3 (s, 3 H, CH_3), 7.93 (d, 1 H, H_6, $J_{5,6}$ = 9 Hz), 8.23 (m, 2 H, $H_{8,11}$), 9.47 (m, 1 H, H_1, $J_{1,2}$ = 9 Hz), 7.2–7.82 (envelope, 5 H, $H_{2,4,5,9,10}$). Anal. ($C_{20}H_{15}NO_2$) C, H, N.

4-Acetoxy-7-methylbenz[*c*]acridine (7i): pale yellow prisms (C_6H_{12}); mp 188 °C; yield 94%; NMR (60 MHz; $CDCl_3$) δ 2.47 (s, 3 H, $COCH_3$), 3 (s, 3 H, CH_3), 8 (d, 1 H, H_6, $J_{5,6}$ = 9 Hz), 8.27 (m, 2 H, $H_{8,11}$), 9.07 (m, 1 H, H_1, $J_{1,2}$ = 9 Hz), 7.23–8 (envelope, 5 H, $H_{2,3,5,9,10}$). Anal. ($C_{20}H_{15}NO_2$) C, H, N.

Biology. In Vivo Carcinogenesis. All compounds were tested by the same standard experimental protocol on 8–10 week old male and female mice of the XVIInc/Z strain. This genetically homogeneous strain shows an extremely low incidence of spontaneous subcutaneous tumors. In a survey of 2500 control animals older than 20 months and of 24 000 control animals older than 15 months, most of them treated with neutral olive oil alone, no subcutaneous tumors were observed. The incidence rate of spontaneous tumors in other tissues among the same control population was also very low (0% mammary tumors, 2.7% hepatomas, 2.6% leukemias, and 20% lung adenomas). The XVIInc/z strain shows a high sensitivity to carcinogenesis by polycyclic aromatic hydrocarbons. Therefore, even one subcutaneous tumor at the site of injection of the PAH is statistically highly significant.

The animals (both males and females) received three subcu-

(30) J. W. Cook and R. Schoental, *J. Chem. Soc.*, 170 (1948).
(31) J. S. Baran, *J. Org. Chem.*, **25**, 257 (1960).

taneous injections, at 4-week intervals, of 0.6 mg of test compound, dissolved in 0.2 mL of neutral olive oil, into the right flank. The animals were monitored weekly by palpation, beginning at the 90th day of the experiment. Animals were killed when they had developed large tumors or at the end of the experiment, at an age of 700–800 days.

All animals were autopsied, and tissues with macroscopically visible modifications were excised for histopathology. All tumors observed were fibrosarcomas at the site of injection. The incidence of other tumors was not significantly different from controls.

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Registry No. **1a**, 3340-94-1; **2a**, 3340-93-0; **3**, 76527-89-4; **4**, 83876-50-0; **5**, 83876-51-1; **6a**, 83876-52-2; **6b**, 83876-53-3; **6c**, 83876-54-4; **7a**, 83876-55-5; **7b**, 83876-56-6; **7c**, 83897-14-7; **7d**, 83876-57-7; **7e**, 83876-58-8; **7f**, 83876-59-9; **7g**, 83876-60-2; **7h**, 83876-61-3; **7i**, 83876-62-4; 5-methyl-1-tetralone, 33892-75-0; 6-methoxy-1-tetralone, 1078-19-9; 7-methoxy-1-tetralone, 6836-19-7; 2-aminoacetophenone hydrochloride, 5468-37-1.

Book Reviews

Progress in Clinical and Biological Research. Volume 71. Psychopharmacology of Clonidine. Edited by Harbans Lal and Stuart Fielding. Alan R. Liss, Inc., New York. 1981. xii + 322 pp. 15.5 × 23.5 cm. ISBN 0-8451-0071-8. $52.00.

This book is a monograph based on a symposium organized by the American Societies for Experimental Biology, held at Anaheim, CA, in April 1980. The symposium focused on the psychopharmacology of clonidine. The book, then, is a compilation of various contributions on the pharmacology of clonidine. In fact, the first third of the book covers recapitulations of the anatomical, biochemical, and pharmacological relations between clonidine and the α receptors in the cardiovascular field. The contribution of Hoefke and Jennewein has the merit of shedding historical light on discussions of the pharmacology of clonidine. Therefore, it is only the second part of this work that really concerns the psychopharmacological properties of clonidine, but even here we encounter neurological data (pains, Korsakoffs' syndrome, etc.).

The review of Lal and Shearman is a timely reminder of the effects of clonidine on most of the classical pharmacological tests; the authors note in particular the sedative, anxiolytic, and antinociceptive effects, the decrease in food intake, and the aggressive behavior triggered off by clonidine. They suggest the therapeutic use of clonidine in particular as an analgesic, in withdrawal symptoms treatment of alcoholism with dementia and anxiety, schizophrenia, and depression.

The following chapters illustrate these various points, insisting, furthermore, on the usefulness of clonidine in the opiate withdrawal syndrome where it is now recognized both pharmacologically and therapeutically. The presumed action mechanism behind this effect is widely discussed in several contributions.

Malik states that clonidine does not always have an antidepressive effect on man.

All in all, this book gives a very interesting, albeit somewhat disparate, glimpse of the various pharmacological properties of clonidine. Certain contributions set out to review some aspects of this pharmacology, which is quite useful. Finally, the interest of clonidine and its action mechanism in the opiate-withdrawal syndrome are largely dealt with, which is by no means the least interesting aspect of the work.

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American Chemical Society Symposium Series. Number 174. *N*-Nitroso Compounds. Edited by R. A. Scanlan and S. R. Tannenbaum. American Chemical Society, Washington, DC. 1981. ix + 400 pp. 15.5 × 23.5 cm. ISBN 0-8412-0667-8. $39.95.

It is now an old joke that *N*-nitroso compounds are potent environmental carcinogens in search of the human cancer they cause. This book admirably reveals why, in spite of the considerable amount of effort put into the study of *N*-nitroso compounds, their role in causing human cancer is still uncertain. Reliable identification and assay of *N*-nitroso compounds down to 0.1 ppb levels in complex biological material is difficult, and much previously published work is of dubious value. The situation with reference to induction of human cancer is complex. In the past, attempts have been made to relate simply total nitrosamine exposure to human cancer, while it is now known that a variety of factors are involved and also that it is not necessarily those nitrosamines present in highest concentrations in the environment that are relevant to the cancer under consideration. Now that the chemical and biological complexities are beginning to be appreciated, an up-to-date book on the subject by workers in the field is especially timely.

The book is an account of the proceedings of the Symposium on *N*-Nitroso Compounds held at the 181st meeting of the American Chemical Society in March 1981 and cosponsored by the Divisions of Agricultural and Food Chemistry and Pesticide Chemistry. It is therefore not unreasonable that, with two exceptions, the 26 presentations describe work carried out in North America or Canada. The papers are well written and provide a pleasing number of formulas, tables, and references. In spite of the fact that the presentations have been published as provided by the authors in "camera-ready" form, there is a good uniform attractive layout.

The book is comprised of three sections. The first relates to the chemistry and metabolism of *N*-nitroso compounds and reveals the still very limited state of understanding of the subject. Thus, while it is generally accepted that α-hydroxylation is a route of metabolism of dimethylnitrosamine, there are large inexplicable interlaboratory differences in estimations of the extent to which α-hydroxylation occurs (Michejda). Papers on metabolism of dipropylnitrosamine (Archer) and of certain cyclic nitrosamines (Hecht) are good accounts of work done, but possible carcinogenic DNA adducts have not yet been identified.

The second and major section of the book discusses the chemistry of formation of *N*-nitroso compounds and factors that block their formation. *N*-Nitroso compounds are formed inadvertently in industry, as discussed for the pesticide (Keefer) and rubber and leather tanning (Fine) industries, in the production beer (Mangino) and of tobacco products (Hoffmann), and in many foods, where ever amines and nitrite comes together under suitable conditions (Gray), in vivo, as in gastric juice (Mergens) and from herbicides in the soil (Khan). The role of bacteria seems to be related to reduction of pH and conversion of nitrate to nitrite rather than to direct catalytic formation of nitrosamines (Ralt). Most important of all is the excellent discussion on the main objective of the whole enterprise, how to reduce human exposure to nitrosamines (Preussmann). It is this application of the work that is very probably reducing the incidence of human cancer at the present time and very amply compensates for slow progress in other areas.

The third section of the book relates to the analysis and oc-