than that of the deoxy derivatives. The corresponding thebaine derivatives have profiles similar to the deoxy compounds but with less analgetic character.

Experimental Section

Melting points were determined on a Kofler hot-plate and are uncorrected. Where analyses are indicated only by symbols of the elements the results obtained for those elements were within ±0.4% of the theoretical values. The structures of all compounds were assigned on the basis of compatible ir and nmr spectra. See Table II for experimental data.

6,14-*endo*-Etheno-7α-ethyltetrahydrooripavine 3*O*-Diethyl Phosphate.—Et_3N (5 ml) was added slowly with vigorous shaking to an ice-cold mixture of 6,14-*endo*-etheno-7α-ethyltetrahydrooripavine[6] (10.8 g), CCl_4 (10 ml), and diethyl phosphite (4.5 ml). The mixture was set aside at room temperature for 18 hr. The mixture was diluted with H_2O and the organic layer separated. The aqueous solution was extracted with $CHCl_3$. The combined organic solutions were washed several times with 1 *N* NaOH and finally H_2O. The dried (Na_2SO_4) extract was evaporated and the residue recrystallized (C_6H_6–petroleum ether) to give 7.0 g (47%) of the phosphate, mp 135–137°. *Anal.* ($C_{26}H_{36}NO_5P$) C, H, N.

(6) K. W. Bentley, D. G. Hardy, J. W. Lewis, M. J. Readhead, and W. I. Rushworth, *J. Chem. Soc. C*, 826 (1969).

The phosphates of the other oripavine derivatives[7] were prepared by analogous procedures and were hydrogenolyzed without purification.

General Procedure for the Hydrogenolysis of the Oripavine Phosphates.—The crude phosphate was dissolved in Et_2O and NH_3 was added (20 ml/g of phosphate); to the mixture Na (2 g-atoms) was added in small pieces, as rapidly as frothing would allow. EtOH (2 mol) was then added and the NH_3 allowed to evaporate. The residue was treated with H_2O and extracted with Et_2O. The combined ethereal extracts were dried (Na_2SO_4) and evaporated. Crystallization of the residue gave the 3-deoxyoripavine.

Biological Methods.—Analgetic activity was determined subcutaneously in the rat tail pressure test of Green and Young[8] and morphine antagonism by the method of Green, Ruffell, and Walton.[9]

Acknowledgments.—The authors thank Mr. Michael Smith for assistance with synthesis, Mr. Cyril Young for preparative tlc, and Dr. Alan L. A. Boura for the pharmacological results.

(7) K. W. Bentley and D. G. Hardy, *J. Amer. Chem. Soc.*, **89**, 3281 (1967).
(8) A. F. Green and P. A. Young, *Brit. J. Pharmacol. Chemother.*, **6**, 572 (1951).
(9) A. F. Green, G. K. Ruffell, and E. Walton, *J. Pharm. Pharmacol.*, **6**, 390 (1954).

Central Nervous System Stimulants of the Xanthone Group

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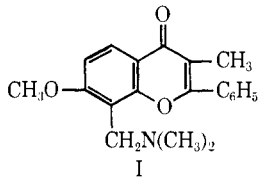
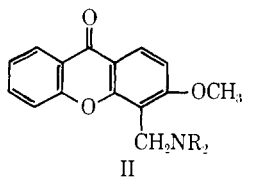
A series of basic derivatives of methoxy-, hydroxy-, and chloroxanthones were synthesized and tested pharmacologically. Some N-disubstituted 4-aminomethyl-3-methoxyxanthones show a powerful CNS stimulating activity. Structure–activity relationships have been examined.

In continuation of our researches[1,2,3] on CNS stimulating drugs of the benzopyrone series, the most significant of which is 3-methyl-7-methoxy-8-dimethylaminomethylflavone (dimefline, I), the xanthone analogs II have now been synthesized.



I



II

This modification of structure I was an outcome of our previous work and was made with the purpose of devising a drug which would reduce some undesirable side effects (such as the excitatory cortical component of the analeptic activity) as well as the toxicity and at the same time improve the clinical safety. The new carrier moiety of the CH_2NR_2 group was to permit a better insight into the structure–activity relationships and to make use of synthetic methods such as addition reactions and partial or total reduction of the CO group, which are more difficult to perform with chromone or flavone analogs.

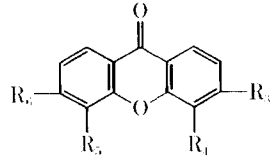
The present work concerns some N-disubstituted 4-aminomethyl derivatives of 3-methoxyxanthone, selected on the basis of previous results[2] in the benzo-γ-pyrone series, as well as the corresponding derivatives of 3-methoxy-6-chloroxanthone, which were prepared in order to take advantage of the possible widening of the safety margin induced by the introduction of Cl.[4] Furthermore, owing to the symmetry of the xanthone molecule we had the opportunity to prepare the bis(aminomethyl) derivatives of 3,6-dihydroxy- and 3,6-dimethoxyxanthone and so to verify the so-called molecular doubling principle,[5] by which one could expect an inversion of the previously observed activity.

A few papers concerning the same subject (preparation of Mannich bases of hydroxyxanthones and alkylated xanthones) have appeared,[6,7,8] but no biological data have been reported. These compounds however, on the basis of our previous findings,[2] ought to be less active than the MeO analogs.

We also wish to report an attempt to apply the

(1) P. Da Re, L. Verlicchi, I. Setnikar, W. Murmann, and M. J. Magistretti, *Nature*, **184**, 362 (1959).
(2) I. Setnikar, W. Murmann, M. J. Magistretti, P. Da Re, and L. Verlicchi, *J. Med. Pharm. Chem.*, **3**, 471 (1961).
(3) P. Da Re, G. Bonola, and L. Verlicchi, *J. Med. Chem.*, **7**, 162 (1964).
(4) A. Burger, "Medicinal Chemistry," 2nd ed., Interscience Publishers Inc., New York, N. Y., 1960, p 43.
(5) A. Lespagnol, *Actual. Pharmacol.*, **6**, 115 (1953).
(6) A. Mustafa, M. M. Sidky, and F. M. Soliman, *Can. J. Chem.*, **41**, 1731 (1963).
(7) Y. S. Agasimundin and S. Rajagopal, *J. Indian Chem. Soc.*, **41**, 471 (1964).
(8) C. S. Angadiyavar, Y. S. Agasimundin, and S. Rajagopal, *J. Karnatak Univ.*, **11**, 52 (1966).

TABLE I
BASIC XANTHONE DERIVATIVES



Compd	R_2	R_4	R_7	R_5	R_6	Mp, °C	Formula[a]	LD_{50} ip in mice (mg/kg)	Relative potency (pentylenetetrazole = 1)	Symptomatology[c]
1	H	OCH_3	$CH_2N(CH_3)_2$	H	H	158–161	$C_{17}H_{17}NO_3$	10.23 (12.47–8.39)	6.93	1
2	H	OCH_3	$CH_2N(C_2H_5)_2$	H	H	101–102	$C_{19}H_{21}NO_3$	43.92 (54.08–35.72)	1.61	1
3	H	OCH_3		H	H	150–152	$C_{20}H_{21}NO_3$	63.56 (72.27–55.89)	1.11	1
4	H	OCH_3		H	H	146–148	$C_{19}H_{19}NO_4$	56.11 (71.85–43.81)	1.26	1
5	H	OCH_3		H	H	172–175	$C_{19}H_{19}NO_3$	58.37 (64.24–52.67)	1.21	1
6	H	OCH_3	$CH_2N(i\text{-}C_3H_7)_2$	H	H	98–99	$C_{21}H_{25}NO_3$	84.38 (90.74–79.58)	0.84	3
7	$CH_2N(C_2H_5)_2$	OCH_3	H	H	H	99–101	$C_{19}H_{21}NO_3$	72.84 (84.22–63.16)	0.97	2
8		OCH_3	H	H	H	120–121	$C_{20}H_{21}NO_3$	122.85 (141.24–100.56)	0.58	2
9	H	OCH_3	$CH_2N(CH_3)_2$	H	Cl	147–149	$C_{17}H_{16}ClNO_3$	124.72 (158.86–117.55)	2.87	2
10	H	OCH_3	$CH_2N(C_2H_5)_2$	H	Cl	134–135	$C_{19}H_{20}ClNO_3$	62.31 (74.79–58.03)	1.14	2
11	H	OCH_3		H	Cl	164–166	$C_{20}H_{20}ClNO_3$	119.89 (138.12–103.04)	0.59	2
12	H	OCH_3		H	Cl	194–196	$C_{19}H_{18}ClNO_4$	*b*		
13	H	OH			OH	208–211	$C_{25}H_{30}N_2O_4$	*b*		
14	H	OH			OH	244–246	$C_{23}H_{26}N_2O_6$	*b*		
15	H	OCH_3	$CH_2N(CH_3)_2$	$CH_2N(CH_3)_2$	OCH_3	151–152	$C_{21}H_{26}N_2O_4$	*b*		
16	H	OCH_3	$CH_2N(C_2H_5)_2$	$CH_2N(C_2H_5)_2$	OCH_3	147–148	$C_{25}H_{34}N_2O_4$	*b*		
17	H	OCH_3			OCH_3	217–218	$C_{27}H_{34}N_2O_4$	*b*		
18	H	OCH_3			OCH_3	265–269	$C_{25}H_{30}N_2O_6$	*b*		
19	H	OCH_3	$CH_2{=}CHCH_2N$ 	H	H	126–127	$C_{22}H_{23}NO_3$	273.68 (301.91–249.67)	0.26	3

[a] All compounds were analyzed for N and compounds **9**–**12** for Cl also, and the analytical results obtained were within ±0.4% of the theoretical values. [b] 300 mg/kg; no convulsions were observed. [c] See text. Numbers refer to paragraphs under CNS stimulating activity.

vinylogy principle[9] to the most potent compounds (Table I, **1–5**) in order to test its validity with regard to the CNS stimulating drugs.

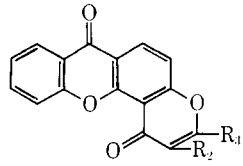
Chemistry.—The derivatives in Table I were prepared by the chloromethylation method.[10] 3-Methoxy, 3-methoxy-6-chloro-, and 3,6-dimethoxyxanthone were treated with formalin, gaseous HCl, or $ClCH_2OCH_3$. This was followed by amination with a secondary base. With 3-methoxyxanthone, 2- and 4-chloromethyl isomers were obtained. The 4-chloromethyl derivative could be easily separated from the reaction mixture by fractional crystallization while the 2 isomer separated only with some difficulty. Better results were obtained by preparative tlc. The structure of the respective derivatives was assigned on the basis of a direct comparison of their transformation products (2- and 4-methyl-3-methoxyxanthone) with authentic samples of these compounds.

With 3-methoxy-6-chloroxanthone, only one $ClCH_2$ derivative was isolated, to which the 4-chloromethyl structure has been assigned. In the chloromethylation of 3,6-dimethoxyxanthone a mixture of isomers was obtained, from which only the 4,5-dichloromethyl derivative was isolated. Its structure was established by comparison with an authentic sample of 3,6-dimethoxy-4,5-dimethylxanthone prepared from 2,2′,4,4′-tetrahydroxy-3,3′-dimethylbenzophenone.

The Mannich reaction applied to 3,6-dihydroxyxanthone seemed to produce a single product to which the same structure as the above bis(aminomethyl) derivatives was assigned.

The vinylog of **3** (Table I) was prepared starting from 3-hydroxy-4-allylxanthone,[11] which was isomerized to the corresponding 4-propenyl derivative by means of KOH in ethylene glycol and then methylated to the 3-MeO derivative. Subsequent bromination with NBS yielded the 3-methoxy-4-(3-bromopropenyl)-xanthone which on condensing with piperidine furnished the vinylog **19** (Table I).

We have also prepared two new 1H,7H-pyrano-[2,3-*c*]xanthene derivatives III and IV, starting with 4-acetyl and 4-propionyl-3-hydroxyxanthone.



III, $R_2 = R_1 = CH_3$
IV, $R_1 = C_2H_5$; $R_2 = H$

Attempts to extend these results to 3,6-dihydroxyxanthone were unsuccessful because of the impossibility of obtaining the 4,5-diacyl intermediates by the Friedel–Crafts or Fries procedures.

Pharmacology. Acute Toxicological Studies.—The main acute toxic effects of analeptics may be considered the result of general hyperexcitation of CNS since these drugs cause both an increase in ventilation and in motor activity; the animals show hyperpnea, hyperexcitability, and clonic and tonic convulsions. While clonic convulsions seem mainly an expression of cortical stimulation[12–14] the tonic component usually prevails in true analeptics brain-stem stimulants.[15–17]

Therefore, in screening tests, two general considerations are valuable: (i) drugs which cause clonic convulsions without tonic extension generally exert little or no analeptic activity; (ii) the centrally acting drugs produce particular types of convulsive patterns which are fairly characteristic of their analeptic properties.[2,18]

Since the paroxysmal excitation of CNS is usually the main cause of death and the toxic syndrome is very acute, the reciprocal value of LD_{50} may be considered as a fairly good index of stimulating activity on CNS and is used to measure the potency ratio with respect to typical brain-stem stimulants, such as pentylenetetrazole.[2]

The acute toxicity was determined intraperitoneally in albino mice employing all the compounds dissolved in saline as HCl salts. The behavior of the animals was observed during 1 day and LD_{50}, referred to the bases, was estimated following the Weil method.[19]

CNS Stimulating Activity.—On the basis of the toxic manifestations and changes of behavior observed with the compounds examined, the following three different patterns stand out.

(1) With very little delay the animals became restless and overexcitable, showed tremors, lost control of body posture, and some tonic–clonic attacks occurred which sometimes alternated with maximal tonic extensions. Within 5–12 min one or two generalized tonic–clonic seizures appeared; soon the tonic component prevailed and a highly characteristic rigidity occurred, the head was flexed on the chest, the forelimbs were extended and rigid. Sometimes after a further paroxysmal convulsive attack, the final stage of maximal tonic extension was followed by death.

This intoxication picture is typical of brain-stem stimulants such as pentylenetetrazole, bemegride, and dimefline[12,18] and was also observed with **1–5**, Table I.

Onset, duration, and type of convulsive pattern were wholly similar to those of pentylenetetrazole as it appears from the relative potency; in fact, except for **1** which is about 7 times more potent, the other compounds are closely related to the reference analeptic. The CNS stimulating potency follows this decreasing order: **1 > 2 > 4 > 5 > 3**.

(2) Within a few minutes the animals became hyperexcitable, trembled, and struggled vigorously. Generalized clonic seizures occurred, but no tonic component, rigidity, or characteristic maximal extension took place. After having lost the coordination capacity, the animals showed a natatory convulsive pattern which progressively declined; within 20 min death occurred, not preceded by maximal tonic extension or severe respiratory depression.

(9) A. Lespagnol and C. Lespagnol, *Chim. Ther.*, 252 (1966).
(10) R. C. Fuson and C. H. McKeever, *Org. React.*, **1**, 63 (1942).
(11) G. S. Puranik and S. Rajagopal, *J. Chem. Soc.*, 1523 (1965).
(12) J. Cheymol, *Actual. Pharmacol.*, **2**, 1 (1950).
(13) L. S. Goodman, M. S. Grewal, W. C. Brown, and E. A. Swinyard, *J. Pharmcol.*, **108**, 168 (1953).
(14) A. Kreindler, E. Zuckermann, M. Steriade, and D. Chimion, *J. Neurophysiol.*, **21**, 430 (1958).
(15) I. Setnikar, W. Murmann, and M. J. Magistretti, *Arzneim. Forsch.*, **11**, 1109 (1961).
(16) T. E. Starzl, W. T. Niemer, and M. Dell, *J. Neuropathol. Exp. Neurol.*, **12**, 262 (1953).
(17) V. G. Longo, "Electroencephalographic Atlas for Pharmacological Research," Elsevier Publishing Co., Amsterdam, 1962.
(18) I. Setnikar, *Res. Progr. Org. Biol. Med. Chem.*, 423 (1964).
(19) C. S. Weil, *Biometrics*, **8**, 249 (1952).

This intoxication picture resembles, therefore, pattern 1 only in the first stage of struggling with regard to both onset and duration (not type) of convulsion; the second stage is rather like the homologous phase of the following pattern 3 as far as convulsion type is concerned.

This picture was observed with 7-11; their order of stimulating activity is the following: **9 > 10 > 7 > 11 > 8**. The potency ratio ranges from 0.5 to 3 times that of pentylenetetrazole.

(3) During the first muscular twitches the animals maintained their posture, but after 10–20 min a few clonic convulsions, often of a natatory type, led them to loss of coordination. Then the animals tended to lie on one side or to assume a catatonic behavior with a staggering gait, and gradually passed into a state of deep depression which led to death.

This picture is similar to that described for niketamide[15] and was observed with **6** and **19**; their potency is low and less than that of pentylenetetrazole.

Conclusions.—Although the experiments reported are not sufficient to elucidate the different mechanism of CNS stimulating action of the 19 xanthone derivatives examined, the following conclusions may be drawn mainly in structure–activity relationships.

(1) By substituting the xanthone molecule for chromone as a carrier moiety in the CNS stimulating N-disubstituted aminomethyl derivatives, the type and degree of activity remain unchanged.

(2) In xanthone derivatives the 3-MeO group which corresponds to position 7 in the chromone molecule, confers an activity which is higher than that of 3-OH analogs prepared according to Agasimundin and Rajagopal[7] and tested for comparison.

(3) The nature of the various N substituents in the aminomethyl chain located in the 4 position of 3-methoxyxanthones, corresponding to position 8 of the chromone derivatives, affects the CNS stimulating activity in a very similar way. The activity seems to decrease gradually as the size of the N substituent increases. The function of the position of the aminomethyl group is emphasized by the lower activity of the 2 isomers.

(4) The introduction of 6-Cl gives an expected[4] decrease of toxicity, but a remarkable modification of the CNS stimulating pattern takes place.

(5) The 4,5-bis(*N*-disubstituted)aminomethylxanthones show neither CNS stimulating activity nor an inversion of this activity, contrary to the so-called molecular doubling principle.[5]

(6) An attempt to verify the vinylogy principle[9] in the active xanthone derivatives led to a strong reduction and change in the pattern of CNS stimulating activity, probably due to the presence of the unsaturated propylene chain.

Experimental Section

All melting points were determined in open glass capillaries, using a Büchi apparatus, and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

The general methods of synthesis described are illustrative of those of analogous compounds.

4- and 2-Chloromethyl-3-methoxyxanthone.—To a solution of 5 g of 3-methoxyxanthone[20] in 50 ml of AcOH, 5 ml of chloromethyl ether was added; the container was stoppered and kept on a steam bath for 4 hr, then left at room temperature overnight. The separated solid was collected, washed (H_2O), and dried. On crystallizing from EtOAc, 3.5 g of white product, mp 214–217°, was obtained. *Anal.* ($C_{15}H_{11}ClO_3$) C, H, Cl.

The mother liquor separated on standing 0.4–0.5 g of the 2-chloromethyl isomer as a white crystalline product, mp 199–200°. *Anal.* ($C_{15}H_{11}ClO_3$) C, H, Cl.

4-Methyl-3-methoxyxanthone.—A solution of 0.5 g of 4-chloromethyl-3-methoxyxanthone in 10 ml of EtOH was hydrogenated over 5% Pd–C, under usual conditions, until H_2 uptake ceased. The solution was filtered from the catalyst and evaporated to dryness. On crystallizing the residue from ligroin 0.35 g of white solid, mp 177–179°, was obtained. A mixture melting point with an authentic sample of 4-methyl-3-methoxyxanthone[21] was not depressed. *Anal.* ($C_{15}H_{12}O_3$) C, H.

2-Methyl-3-methoxyxanthone.—In a similar manner 2-chloromethyl-3-methoxyxanthone yielded the corresponding 2-Me derivative as a white product, mp 160–161°. *Anal.* ($C_{15}H_{12}O_3$) C, H.

3-Methoxy-4-dimethylaminomethylxanthone.—To a solution of 2.7 g of 3-methoxy-4-chloromethylxanthone in 20 ml of PhH, a small excess of Me_2NH was added, the flask was stoppered and the mixture kept on a steam bath for 4 hr. After evaporation of the solvent the residue was taken up in H_2O and the separated base extracted with $CHCl_3$. The $CHCl_3$ layer was washed with saturated NaCl solution, dried, and filtered. Removing of the solvent left a residue which on crystallizing from EtOAc gave 2.1 g of a white product, mp 158–161°. *Anal.* ($C_{29}H_{21}NO_3$) N.

3-Methoxy-6-chloro-4-chloromethylxanthone.—A mixture of 3 g of 3-chloro-6-methoxyxanthone,[20] 0.3 g of paraformaldehyde in 25 ml of AcOH, and 20 ml of HCl, was stirred at 70° for 2 hr, during which time a stream of HCl gas was introduced. The reaction mixture was then poured into ice-H_2O and the separated solid was collected, washed (H_2O), and dried. The crude product on crystallizing from EtOAc gave 1.7 g of white solid, mp 229–230°. *Anal.* ($C_{15}H_{10}Cl_2O_3$) C, H, Cl.

3,6-Dihydroxy-4,5-bis(piperidinomethyl)xanthone.—To a solution of 2.28 g of 3,6-dihydroxyxanthone[22] in 50 ml of EtOH 1.7 g of piperidine and 3 ml of 40% CH_2O were added and the reaction mixture was kept at 70° for 7 hr. After evaporation of the solvent the residue was extracted with $CHCl_3$, washed (H_2O), and dried. Removing of the solvent left a residue which on crystallizing from ligroin gave 1.5 g of white solid, mp 208–211° dec. *Anal.* ($C_{25}H_{30}N_2O_4$) N.

3,6-Dimethoxy-4,5-bis(chloromethyl)xanthone.—A mixture of 2.5 g of 3,6-dimethoxyxanthone,[22] 50 ml of AcOH, 25 ml of HCl, and 1 g of paraformaldehyde, was stirred at 70° for 5 hr while a stream of HCl gas was introduced. The reaction mixture was then poured into H_2O and the separated solid was collected, washed (H_2O), and dried. On crystallizing the crude product from EtOAc, 2 g of white solid, mp 263–266°, was obtained. *Anal.* ($C_{17}H_{14}Cl_2O_4$) C, H, Cl.

3,6-Dimethoxy-4,5-dimethylxanthone. A.—A solution of 0.5 g of 3,6-dimethoxy-4,5-dichloromethylxanthone in 10 ml of THF were hydrogenated over 5% Pd–C until H_2 uptake ceased. The solution was filtered from the catalyst and evaporated to dryness. The residue on crystallizing from EtOH gave 0.3 g of white crystalline product, mp 255–256°. *Anal.* ($C_{17}H_{16}O_4$) C, H.

B.—To a solution of 0.5 g of 3,6-dihydroxy-4,5-dimethylxanthone (*vide infra*) in 20 ml of Me_2CO, 2 g of K_2CO_3 and 1 ml of Me_2SO_4 were added and the mixture was refluxed for 4–5 hr. After filtration the solvent was removed and the residue suspended in NaOH. The insoluble fraction was collected, washed (H_2O), and dried. On crystallizing from EtOH, 0.35 g of white product, mp 254–255°, was obtained. *Anal.* ($C_{17}H_{16}O_4$) C, H.

The products described under A and B were found to be identical by ir comparison.

2,2′,4,4′-Tetrahydroxy-3,3′-dimethylbenzophenone.—A mixture of 2.5 g of 2,4-dihydroxy-3-methylbenzoic acid,[23] 2.5 g of 2-methylresorcinol, 10 g of freshly fused $ZnCl_2$, and 18.5 ml of $POCl_3$, was heated at 80–90° for 45 min, or kept at room temperature for 48 hr. The reaction mixture was poured into H_2O

(20) A. A. Gottberg and A. H. Wragg, *J. Chem. Soc.*, 4227 (1958).
(21) Y. S. Agasimundin and S. Rajagopal, *Monatsh. Chem.*, **97**, 423 (1966).
(22) P. K. Grover, G. D. Shah, and R. C. Shah, *J. Chem. Soc.*, 3892 (1955).
(23) R. C. Shah and M. C. Taiwatia, *ibid.*, 1828 (1938).

and the separated solid was collected by filtration, washed repeatedly (H_2O), and dried. On crystallizing from boiling H_2O, 3.2 g of an orange-colored product, mp 174–175° was obtained. *Anal.* ($C_{15}H_{16}O_5$) C, H.

3,6-Dihydroxy-4,5-dimethylxanthone.—Following the procedure of Grover, *et al.*,[22] 2.5 g of 2,2′,4,4′-tetrahydroxy-3,3′-dimethylbenzophenone in 25 ml of H_2O, was heated in an autoclave at 200–220° for 2.5 hr. After cooling the 3,6-dihydroxy-4,5-dimethylxanthone was collected and dried. It did not melt below 310°. *Anal.* ($C_{15}H_{14}O_4$) C, H.

3-Propionoxyxanthone.—A mixture of 4 g of 3-hydroxyxanthone[24] and 10 ml of Pr_2O was refluxed for 1 hr and then poured into ice-H_2O. The separated solid was collected by filtration, washed (H_2O), and dried. On crystallizing from ligroin, 3.1 g of white solid, mp 151–152°, was obtained. *Anal.* ($C_{16}H_{12}O_4$) C, H.

3-Hydroxy-4-propionylxanthone.—To a melt consisting of 1 g of NaCl and 3 g of $AlCl_3$, 1 g of 3-propionoxyxanthone was added and the temperature was kept at 160–170° for 4.5 min. The mixture was hydrolyzed with dil HCl and ice-H_2O, and the separated solid was collected and washed with H_2O. This was dissolved in dil NaOH and reprecipitated with dil HCl. The separated solid, on crystallizing from EtOH, gave 0.8 g of white product, mp 170–172°. *Anal.* ($C_{16}H_{12}O_4$) C, H.

(24) F. Ullmann and W. Denzler, *Chem. Ber.*, **39**, 4335 (1906).

2,3-Dimethyl-1H,7H-pyrano[2,3-*c*]xanthene-1,7-dione (III).—A mixture of 0.6 g of 3-hydroxy-4-propionylxanthone, 0.7 g of anhyd NaOAc, and 3 g of Ac_2O was refluxed for 8 hr. By pouring the reaction mixture into H_2O a solid was isolated, which on crystallizing from EtOH, gave 0.5 g of white product, mp 266–267°. *Anal.* ($C_{18}H_{12}O_4$) C, H.

3-Hydroxyxanthonyl-(4)-styril Ketone.—To a solution of 0.5 g of 3-hydroxy-4-acetylxanthone[25] and 0.2 ml of BzH in 30 ml of 95% EtOH, 5 ml of 50% aqueous KOH was added with stirring, and the mixture was left to stand 12 hr. After dilution with H_2O and acidification, the separated solid was collected, dried, and crystallized from ligroin yielding 0.5 g of light yellow product, mp 172–175°. *Anal.* ($C_{22}H_{14}O_4$) C, H.

3-Phenyl-1H,7H-pyrano-[2,3-*c*]xanthene-1,7-dione (IV).—A mixture of 0.2 g of the preceding product, 0.3 g of SeO_2, and 7 ml of AmOH was heated at 145° for 7 hr. After cooling, the reaction mixture was filtered and the collected solid (a mixture of Se and product) was extracted with EtOH to give 0.15 g of white solid, mp 272–273°. *Anal.* ($C_{22}H_{12}O_4$) C, H.

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(25) Y. S. Agasimundin and S. Rajagopal, *J. Org. Chem.*, **30**, 2084 (1965).

Thia Steroids. III. Derivatives of 2-Thia-A-nor-5α-androstan-17β-ol As Probes of Steroid–Receptor Interactions[1]

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The preparation of analogs of 2-thia-A-nor-5α-androstan-17β-ol having three typical modifications used in anabolic–androgenic compounds, *viz.*, the introduction of a 7α-Me group, the 19-nor modification, and the introduction of a 17α-alkyl group, is described. In addition, the SO and SO_2 derivatives of the parent compound were prepared. Biological evaluation shows that the SO and SO_2 derivatives are inactive, and that the pharmacological effects of the other modifications on thiasteroids parallels their effects in the testosterone series. From this it is concluded that the three modifications affect drug–receptor interactions, and not drug distribution or drug metabolism. The effects of these groups may be direct, by interaction with the receptor, or indirect, by altering the conformation of the steroid itself through conformational transmission.

In a previous paper[2] of this series, the synthesis of 2-thia-A-nor-5α-androstan-17β-ol as an isostere of 17β-hydroxy-5α-androst-2-ene was described. The androgenic–anabolic activity of this compound was taken as evidence that *steric* effects, and not *electronic* factors, are important in connection with structural requirements at C-2 and/or C-3 in androgens. As described in the Discussion, the discovery of this new, biologically active ring system provides a powerful general tool in the examination of the relationship between chemical structure and biological activity in androgenic–anabolic steroids. For this reason, the preparation of thiasteroids having three typical enhancing groups used in anabolic–androgenic compounds, *viz.*, the 7α-Me group, the 19-nor modification, and the 17α-alkyl group, was undertaken. In addition, the sulfoxide and sulfone derivatives of 2-thia-A-nor-5α-androstan-17β-ol acetate were synthesized.

7α-Methyltestosterone[3] was prepared in 40% yield by an improved procedure and the reduction of the double bond in this compound was studied. Hydrogenation in the presence of PtO_2 gave a product which had a negative CD curve and a negative Cotton effect in the ORD. It was assigned the 5β configuration **2** on this basis.[4] The formation of **2** under these conditions is consistent[5] with interference by the axial 7α-Me group to adsorption of the α face of the steroid on the catalyst surface. By contrast, reduction of 7α-methyltestosterone with Li in liquid NH_3 cleanly gave the 5α-dihydro compound **3**, as shown by the positive CD and Cotton effect curves of the corresponding acetate **4**. The formation of **3** under conditions giving the thermodynamically favored isomer is in accord with the repulsive interaction in **2** of the 7α-Me group and the 1α-H, which is absent in **3**.

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(2) M. E. Wolff and G. Zanati, *J. Med. Chem.*, **12**, 629 (1969).

(3) J. A. Campbell and J. C. Babcock, *J. Amer. Chem. Soc.*, **81**, 4069 (1969).

(4) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *ibid.*, **83**, 4013 (1969).

(5) R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine, and R. R. Whetstone, *ibid.*, **64**, 1985 (1942).