The Analgetic Activity of 4a,8a-(Methaniminomethano)naphthalene Derivatives

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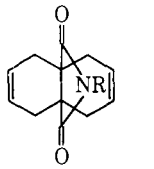
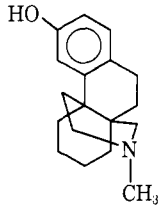
As a continuation of the synthetic and pharmacological studies which revealed the significant anticonvulsant activity of 1,4,5,8-tetrahydro-4a,8a-naphthalenedicarboximide (I), a number of the corresponding tricyclic amines have been prepared and studied for analgetic activity. The amines were prepared by $LiAlH_4$ reduction of the corresponding dicarboximides. Three of these compounds, X, XI, and XV, displayed potent activity in the HCl writhing test but the toxicity of the entire series was consistently high, and low therapeutic ratios resulted. No other activity was revealed in the general pharmacological screen.

As a continuation of the synthetic and pharmacological studies which revealed the significant anticonvulsant activity of 1,4,5,8-tetrahydro-4a,8a-naphthalenedicarboximide (I),[1] a number of the corresponding tricyclic amines have been prepared. The low toxicity seen in the dicarboximides encouraged the hope that these amines would have new biological properties with good therapeutic ratios. In addition, the literature describes several similar compounds which possess biological activity of interest.

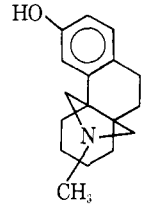


I, R = H
XII, R = CH_2—△

Kugita[2] prepared the morphine analogs II and III and found II to have analgetic and antitussive action but not as powerful as anticipated. Compound III,

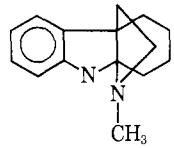


II

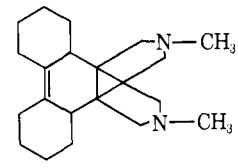


III

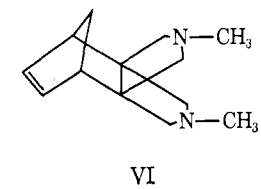
however, was not analgetic and was five times more toxic than morphine. Boehringer Sohn[3] reported analgetic activity for the iminoethanocarbazole IV. Recently, Welner and Ginsburg[4] prepared V and VI as a potential analgetics but these were shown to be inactive.



IV

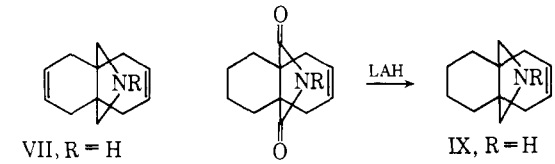


V



VI

$LiAlH_4$ reduction of I in refluxing tetrahydrofuran for 3 days produced 1,4,5,8-tetrahydro-4a,8a-(methaniminomethano)naphthalene (VII) which was purified as the hydrochloride. This amine demonstrated potential analgetic activity in the HCl writhing test with an ED_{50} of 50 mg/kg. However, it was also



VII, R = H
X, R = CH_3
XIII, R = CH_2—△

VIII

IX, R = H
XI, R = CH_3

quite toxic, the test mice showing skeletal muscle weakness and ataxia at doses of 100 mg/kg.

The hexahydrodicarboximide VIII, which was essentially inactive as an anticonvulsant, was reduced in a similar manner and the resulting amine IX was isolated as the crystalline hydrochloride. This compound was completely inactive in the HCl writhing test but still toxic, because even 50-mg/kg doses caused skeletal muscle weakness in the mice. Neither of these amines demonstrated any other significant activity in the pharmacodynamic screen.

In an effort to increase the analgetic properties and perhaps reduce the toxicity, the corresponding N-methyl analogs of VII and IX were synthesized. These amines X and XI were obtained in best yield by reduction of the N-methyldicarboximides.

This modification did, indeed, sharply increase the potency of both compounds. The ED_{50} of X showed a tenfold decrease to 4.6 mg/kg. Amine XI was about half as active as X with an ED_{50} of 10.0 mg/kg. Unfortunately, although the toxicity did not increase at the same ratio, both compounds remained highly toxic with LD_{50} values of 56.2 mg/kg for X and 68.1 mg/kg for XI.

Because of the high analgetic potency of the morphine antagonists containing cyclopropylmethyl substitution on nitrogen,[5] the corresponding amine was prepared in

(1) E. R. Wagner and A. D. Rudzik, *J. Med. Chem.*, **10**, 607 (1967).

(2) H. Kugita, *Pharm. Bull.* (Tokyo), **4**, 29 (1956); *Chem. Abstr.*, **51**, 1992*d* (1957).

(3) C. H. Boehringer Sohn, German Patent 1,205,105 (1965); *Chem. Abstr.*, **64**, 6657 (1966).

(4) S. Welner and D. Ginsburg, *Israel J. Chem.*, **4**, 39 (1966); see also J. Altman, E. Babad, J. Itzchaki, and D. Ginsburg, *Tetrahedron, Suppl.*, (1) **8**, 279 (1966), for the preparation of some similar compounds.

(5) L. S. Harris, *Ann. Rept. Med. Chem.*, *1965*, 44 (1966).

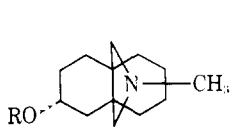
TABLE I

Text no.	Formula[a]	Mp, °C	% yield	Screening dose, mg/kg	HWF	LD_{50}, mg/kg	LD_{50}, mg/kg
VII	$C_{12}H_{17}N \cdot HCl$	282–283	50	50	4/4	50 (41.0–61.0)	100
IX	$C_{12}H_{19}N \cdot HCl$	274–275	22	50	0/4		100
X	$C_{13}H_{19}N \cdot HCl$	162–165	67	50	4/4	4.64 (1.82–11.8)	100
XI	$C_{13}H_{21}N \cdot HCl$	187–189	82	50	4/4	10.0 (2.46–40.6)	68.1
XIII	$C_{16}H_{23}N \cdot HCl$	208–209	42	100	1/4		56.2
XV	$C_{20}H_{27}NO_2 \cdot HCl$[b]	207–209	21	10	4/4	5.99 (2.69–13.3)	46.4
XVII	$C_{20}H_{27}NO_2 \cdot HCl$	230–232	5	10	0/4		68

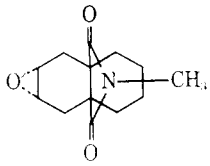
[a] All compounds were analyzed for C, H, N, Cl. [b] The analyses were performed after drying at 110°. [c] HCl writhing test.

this series. By reduction of the N-cyclopropylmethyldicarboximide (XII) (which was inactive as an anticonvulsant against pentylenetetrazole), N-cyclopropylmethyl-1,4,5,8-tetrahydro-4a,8a-(methanaminomethano)naphthalene (XIII) was obtained and purified as the hydrochloride. This was inactive in the HCl writhing test and also inactive as a morphine antagonist. The toxicity (LD_{50} = 56.2 mg/kg) was similar to that of X and XI.

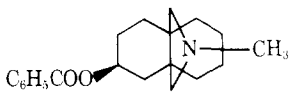
One other compound in this series was found to have potent analgetic activity in the HCl writhing test. This was the benzoate ester XV of the tricyclic amino alcohol XIV.



XIV, R = H
XV, R = COC_6H_5



XVI



XVII

Reduction of the epoxy-N-methyldicarboximide XVI with a large excess of $LiAlH_4$ produced an oily amino alcohol which would not form a crystalline hydrochloride. A benzoate ester, formed with benzoyl chloride, was converted to the hydrochloride and chromatographed on silicic acid to isolate two isomeric crystalline amino ester salts. The predominate isomer (21% yield) was assigned structure XV and the other (5% yield) was designated structure XVII on the basis of the synthetic route. Although no rigorous proof has been made, steric factors would cause the predominate epoxide isomer to be XVI and thus the most abundant amino ester should be XV.

The amino ester hydrochloride XV had an ED_{50} of 5.99 mg/kg in the HCl writhing test but a toxicity of 46.4 mg/kg. The other isomer XVII was completely inactive, but also still toxic (LD_{50} = 68 mg/kg). Neither compound displayed any activity against oxotremorine or in any other test in the pharmacodynamic screen.

It is apparent that reduction of the tricyclic 4a,8a-naphthalenedicarboximides to the amines produces compounds with potent analgetic activity in the writhing test, but the favorable toxicity seen in the dicarboximides is lost and low therapeutic ratios result. The toxicity appears to be quite general for all the amines despite a much larger variation in analgetic activity. None of these compounds displayed any other activity in the general pharmacological screen.[6]

Experimental Section[7]

Chemistry. 1,4,5,8-Tetrahydro-4a,8a-(methaniminomethano)naphthalene Hydrochloride (VII).—1,4,5,8-Tetrahydro-4a,8a-naphthalenedicarboximide (I)[1] (6.1 g, 0.33 mole) was reduced by refluxing for 3 days in 200 ml of THF with 5.1 g (0.133 mole) of $LiAlH_4$. The excess hydride was decomposed with *i*-PrOH and saturated NaCl solution. The salt layers were washed with CH_2I_2 and, after removal of the solvents, the oily residue was converted to the hydrochloride by precipitation from Et_2O solution with HCl gas. Recrystallized from MeOH–Et_2O, the amine hydrochloride weighed 3.6 g (see Table I for physical constants and yields).

The ir and nmr spectra were consistent with the proposed structure. In the nmr spectrum (D_2O), the eight allylic CH_2 protons formed a narrow multiplet at 2.11 ppm which was coupled (J = 1.5 cps) to the vinyl protons, a multiplet at 5.60 ppm (J = 1.5 cps). The heterocyclic methylene protons appeared as a singlet at 3.25 ppm. This is consistent with the spectra reported by Snatzke and Zanati[8] and Bloomfield and Smiley Irelan[9] for similar compounds.

1,2,3,4,5,8-Hexahydro-4a,8a-(methaniminomethano)naphthalene hydrochloride (IX) was prepared in an exactly analogous manner from 1,2,3,4,5,8-hexahydro-4a,8a-naphthalenedicarboximide (VIII). The ir spectrum was consistent with the proposed structure. The nmr spectrum (D_2O) showed the eight protons of the saturated ring as a singlet at 1.5 ppm, the four vinyl protons as a broadened singlet at 2.6 ppm, the four protons of the hetero ring as a broadened AB quartet centered at 3.23 ppm and the vinyl protons as a multiplet at 5.67 ppm.

Compounds X, XI, and XIII described in Table I were all prepared in a similar fashion from the corresponding dicarboximides.

N-Cyclopropylmethyl-1,4,5,8-tetrahydro-4a,8a-naphthalenedicarboximide (XII).—The dicarboximide precursor of XIII was prepared in 20% yield by slow heating of a mixture of 10 g of 1,4,5,8-tetrahydro-4a,8a-naphthalenedicarboxylic anhydride, 5.3 g of cyclopropylmethylamine hydrochloride, 3 g of K_2CO_3, and 5 ml of H_2O to 190°. The resulting residue was treated with 100 ml of H_2O and the dicarboximide separated. Recrystallized from EtOH it weighed 2.7 g, mp 91–92°. Its spectra were consistent with the dicarboximide structure.

Octahydro-10-methyl-4a,8a-(methaniminomethano)naphth-2-yl Benzoate Hydrochlorides (XV and XVII).—N-Methyl-1,2,3,4,5,8-hexahydro-4a,8a-naphthalenedicarboximide (10 g) was epoxidized with *m*-chloroperbenzoic acid as described previously[1] and then reduced with excess $LiAlH_4$ in refluxing THF for 3 days.

(6) The pharmacological tests (hexobarbital sleep time (HST), maximal electroshock (MES), strychnine lethality (SLT), and pentylenetetrazol (MET)) were described in ref 1. There was also no activity against oxotremorine-induced tremors.

(7) All microanalyses were performed by Midwest Microlab., Inc., Indianapolis, Ind. Analyses are indicated only by symbols of the elements; analytical results obtained for those elements were within ±0.4% of the theoretical values. All melting points were obtained on a Thomas–Hoover Unimelt apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer grating infrared spectrophotometer Model 337. Nmr spectra were obtained using a Varian A-60 nmr spectrometer.

(8) G. Snatzke and G. Zanati, *Tetrahedron*, **684**, 62 (1965).

(9) J. J. Bloomfield and J. R. Smiley Irelan, *J. Org. Chem.*, **31**, 2017 (1966).

The amino alcohol, isolated as described above, was dissolved in Et_2O and treated with HCl gas to precipitate the amorphous hydrochloride. This crude salt was dissolved in 100 ml of $CHCl_3$ and 5 g of benzoyl chloride was added. The reaction was allowed to stand for 10 min, and then the solvents were removed *in vacuo*. The resulting oil, after standing for another 3 days, was warmed on the steam bath for 0.5 hr. The mixture was suspended in Et_2O and washed (K_2CO_3, H_2O). The Et_2O solution, dried over K_2CO_3, was removed *in vacuo*. The resulting yellow syrup (11.3 g) showed no OH absorption in the ir but a strong ester carbonyl.

The oil was reconverted to the hydrochloride in Et_2O as before. Removal of the solvents left a dry foam. Part of this foam (2 g) was converted to a maleate salt, but though crystalline, it was highly hygroscopic.

The remainder of the foam was chromatographed on 200 g of silicic acid (Mallinckrodt chromatography grade 200 mesh, Me_2CO washed and dried). The column was eluted with $CHCl_3$. The first 2.25 l. removed noncrystalline materials. The next 1.25 l. eluted 5.6 g of a solid which when crystallized twice from MeOH–Et_2O produced 4.0 g of ester hydrochloride XV (lost solvent at 102–103°, remelted 207–209°). Liberated as the free base and recrystallized from EtOH–H_2O, it melted at 77–78°.

The remainder of the material eluted from the column weighed 1.8 g, which on recrystallization from MeOH–Et_2O produced 0.9 g of isomer XVII, mp 230–232° (free base mp 91–93°). The ir and nmr spectra were consistent with the proposed structures XV and XVII.

Pharmacology.—Adult male mice weighing 18–24 g were used in all the pharmacological testing. ED_{50} values were calculated by the method of Litchfield and Wilcoxon.[10] See Table I for a summary of the pharmacological results.

HCl Writhing Test (HWT).—Groups of four mice were injected subcutaneously with the test compound and 45 min later, 0.01 ml/g of a 0.1% aqueous solution of HCl was administered intraperitoneally. The mice were then observed for 10 min for prevention of writhing. The results are expressed as the ratio of the number of mice protected to the number of mice tested.

Acknowledgments.—We wish to sincerely thank Dr. A. D. Rudzik and Mr. Phil Shea for obtaining the pharmacological test data.

(10) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949).

Synthesis and Antiinflammatory Screening of Phenoxazine-1-carboxylic Acids

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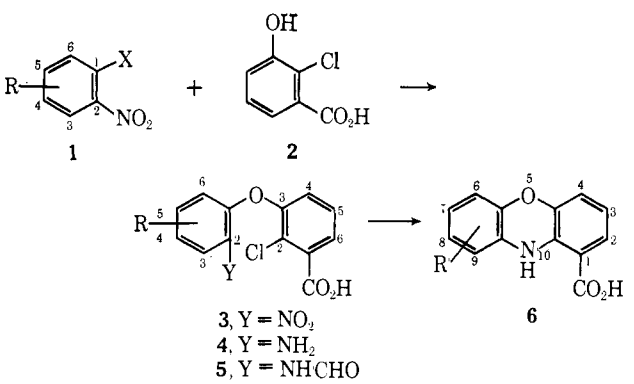
The title compounds (**6a–x**) were prepared in four steps from 1-halo-2-nitrobenzenes (1) and 2-chloro-3-hydroxybenzoic acid (2). Antiinflammatory activity was determined using the guinea pig uv erythema assay and the carrageenin filter paper granuloma assay in adrenalectomized rats. In these assays the most active compound, **6d**, was less active than the isosteric 8-trifluoromethylphenothiazine-1-carboxylic acid.

The recent finding in our laboratories that 8-trifluoromethylphenothiazine-1-carboxylic acid[1] has interesting antiinflammatory activity in experimental animals prompted us to investigate the isosteric phenoxazine compound. When this too had interesting biological activity further chemical studies were planned in which two goals were established: (1) to prepare a wide variety of 8-substituted phenoxazine-1-carboxylic acids, and (2) to investigate the effect on biological activity of moving the trifluoromethyl group from positions 6–9 in phenoxazine-1-carboxylic acid.

Early attempts to prepare **6d** using the Smiles rearrangement in an effort to utilize the procedure developed for the preparation of the phenothiazine-1-carboxylic acids[1] were unsuccessful. Under these reaction conditions the intermediate, 2-amino-4-trifluoromethylphenol, lost fluoride ion and apparently polymerized.[2] Therefore, a route used previously with success in our laboratories[3] was employed for the preparation of the compounds reported (Scheme I).

If, in addition to the nitro group, **1** contained a second electron-withdrawing group *ortho* or *para* to the halogen being displaced, diphenyl ether formation proceeded readily. With an electron-releasing group in the same positions the reaction proceeded poorly or failed. Only with DMF as a solvent were yields usually satisfactory (even with DMF 4-chloro-3-nitroanisole failed to react). If the fluoro compound (**1**, X = F) was available yields were improved and bis(2-methoxyethyl) ether (diglyme) could be substituted for DMF (*e.g.*, **3k**, Table I). The nitrodiphenyl ethers (**3**) are listed in Table I.

SCHEME I



Reduction of **3** gave the amines **4** (Table II) which were formylated to give **5** (Table III). For the most part, these reactions were straightforward. However, in a few instances (**4b** and **v** and **5a**, **e**, **u**, **v**, and **w**) we were unable to obtain analytically pure samples, although impure **4b** could be converted to analytically pure **5b**. Attempts to hydrolyze purified **5b** to **4b** resulted in the concomitant hydrolysis of the trifluoromethyl group and the isolation of an amino diacid (**4**, R = 3-CO_2H). Ring closure and hydrolysis of the N-formyl group of **5** to yield **6** (Table IV) were usually effected simultaneously in refluxing DMF in the presence of copper bronze. Under these conditions

(1) B. M. Sutton and J. H. Birnie, *J. Med. Chem.*, **9**, 835 (1966).
(2) M. R. Pettit and J. C. Tatlow, *J. Chem. Soc.*, 3852 (1954).
(3) M. P. Olmsted, P. N. Craig, J. J. Lafferty, A. M. Pavloff, and C. L. Zirkle, *J. Org. Chem.*, **26**, 1901 (1961).