Synthesis of Compounds with Potential Psychotomimetic Activity. IV[1,2a]

EDWARD R. FREITER, JOSEPH G. CANNON,[2b] LARRY D. MILNE,

Laboratory of Medicinal Chemistry, College of Pharmacy, The University of Iowa, Iowa City, Iowa 52240

AND LEO G. ABOOD

Center for Brain Research, University of Rochester, Rochester, New York 14627

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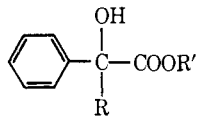
As a continuing study of structure–activity relationships of psychotomimetic agents, the N-methyl-3-piperidyl esters of cycloheptylphenylglycolic acid, ethynylphenylglycolic acid, and of acids derived from 1,2,3,3a,8,8a-hexahydrocyclopent[*a*]indene were prepared. A new and improved method of esterification of disubstituted glycolic acids, involving treatment of their sodium salts with N-methyl-3-piperidyl tosylate, has been utilized. The methyl ester of 9-hydroxy-9a-methyl-1,2,3,4,4a,9a-hexahydrofluorene-9-carboxylic acid has been prepared, but extremely low yields did not permit further work with this compound. Biological test data are reported.

An earlier communication from this laboratory[1] reported preparation of ethynylphenylglycolic (**1a**) and cycloheptylphenylglycolic (**2a**) acids as precursors to their N-methyl-3-piperidyl esters (**1** and **2**) which were to be evaluated as hallucinogens. Attempts to prepare

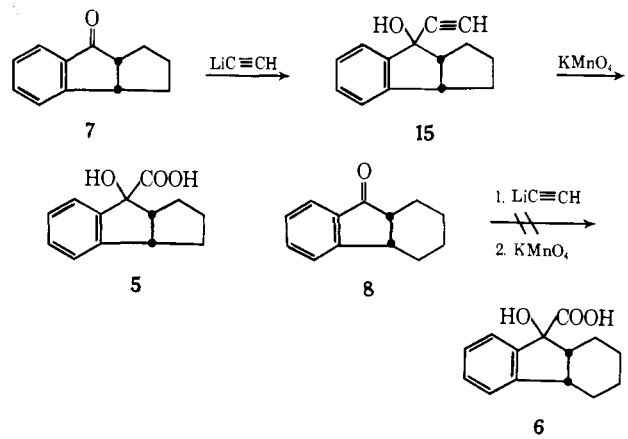


1, R = ethynyl; R′ = N-methyl-3-piperidyl
1a, R = ethynyl; R′ = H
2, R = cycloheptyl; R′ = N-methyl-3-piperidyl
2a, R = cycloheptyl; R′ = H
3, R = ethyl; R′ = N-methyl-3-piperidyl
4, R = vinyl; R′ = N-methyl-3-piperidyl

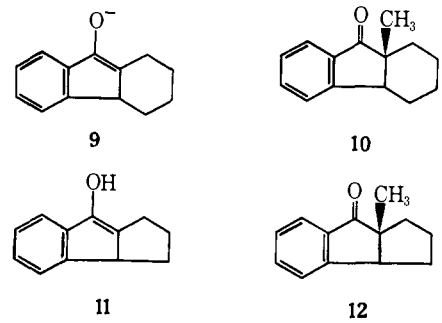
1 and **2** failed; however, N-methyl-3-piperidyl ethylphenylglycolate **3** and vinylphenylglycolate **4** were synthesized and both were shown to possess some degree of central effect in mouse hyperactivity and swimming maze tests.

The present work was aimed at finding a synthetic route to the N-methyl-3-piperidyl esters of ethynylphenyl- and cycloheptylphenylglycolic acids **1** and **2**. In addition, it was desired to prepare N-methyl-3-piperidyl esters of two new acids, 8-hydroxy-1,2,3,3a,8,8a-hexahydrocyclopent[*a*]indene-8-carboxylic acid (**5**) and 9-hydroxy-1,2,3,4,4a,9a-hexahydrofluorene-9-carboxylic acid (**6**). Synthesis of **5** and **6** was proposed from the corresponding ketones **7** and **8**, by means of an ethynylation followed by oxidation of the triple bond, according to a method utilized earlier in this laboratory[3] (Scheme I). Attempts to ethynylate the ketonic group of **8** resulted only in quantitative recovery of starting material; a single attempt to perform a Reformatsky reaction on **8** similarly led to recovery of starting material. On the basis of earlier studies[4] it is concluded that the basicity of the organometallic reagent caused the rapid formation of the enolate ion **9** which is inert toward the alkylating reagent. It was proposed that introduction of a methyl group at position 9a (structure **10**) would prevent

SCHEME I



enolization and should permit ethynylation of the ketonic group. Dreiding models indicated that the enolic form **11** would be a highly strained system and



would be unfavored sterically. It was predicted that **7** would react normally with metallic acetylides; however, introduction of an angular methyl group at position 8a (compound **12**) might result in a final product of some biological interest. The angularly methylated ketones **10** and **12** have been reported in the literature,[5,6] but by procedures which do not involve direct alkylation of the parent ketones. Compound **8**, when treated with potassium *t*-butoxide and methyl iodide, reacted smoothly to give a product whose nmr spectrum verified the presence of a C-methyl group. When **7** was subjected to the same conditions, an approximately equal mixture of starting

(1) Part III: R. J. Adamski and J. G. Cannon, *J. Med. Chem.*, **8**, 444 (1965).

(2) (a) This investigation was supported in part by Grant MH 07775, National Institute of Mental Health. Abstracted in part from a thesis submitted by E. R. F. in partial fulfillment of the requirements for the degree of Doctor of Philosophy, University of Iowa, 1967 (b) To whom all correspondence should be directed.

(3) S. B. Kadin and J. G. Cannon, *J. Org. Chem.*, **27**, 240 (1962).

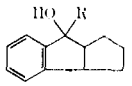
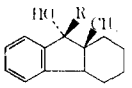
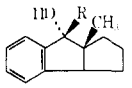
(4) R. J. Adamski and J. G. Cannon, *ibid.*, **29**, 3693 (1964).

(5) M. S. Newman, G. Eglinton, and H. M. Grotta, *J. Am. Chem. Soc.*, **75**, 349 (1953).

(6) M. Protiva and L. Novák, *Chem. Listy*, **47**, 881 (1953).

TABLE I

ETHYNYL ALCOHOLS AND METHYL ESTERS OF GLYCOLIC ACIDS

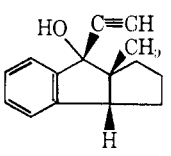
Structure	R	Mp or bp, °C	Yield, %	Formula	Analyses
	C≡CH (**15**)	76–78[a]	58	$C_{10}H_{12}O$	C, H
	$COOCH_3$	75–77[b]	11	$C_{13}H_{16}O_3$	C, H
	C≡CH (**14**)	74–76[c]	85		C, H[d]
	$COOCH_3$	78–79[e]	1	$C_{14}H_{20}O_3$	C, H
	C≡CH[f] (**13**)	140 (0.025 mm)[g]	73		C, H[h]
	$COOCH_3$	90–91[i]	8[c]	$C_{13}H_{18}O_3$	C, H

[a] Recrystallized from MeOH–Skelley B. [b] Recrystallized from Skelley B. [c] Calculated on the amount of ethynyl alcohol. [d] Analysis of Hg complex: $(C_{16}H_{18}O)_2Hg$. [e] Separated on silicic acid column using 9:1 cyclohexane–EtOAc as the eluent; recrystallized from H_2O–MeOH. [f] Reaction temperature was raised to 55° for 2.5 hr. [g] $n^{25}D$ 1.5541. [h] Analysis of Hg complex: $(C_{15}H_{16}O)_2Hg$. [i] Separated on a silicic acid column using 15:1 cyclohexane–EtOAc as the eluent; recrystallized from H_2O–MeOH.

material and methylated product was obtained. Repeated methylation of this reaction mixture resulted, after the fourth treatment, in a product which was shown by gas chromatography and nmr data to be the pure methylated product. An attempt to C-methylate **7** with potassium metal and methyl iodide was not satisfactory.

It may be assumed that the methyl group entered the less hindered side of the ketone molecules. In the case of the cyclopent[*a*]indanone system **7**, the methyl group would be expected to enter *cis* to the hydrogen at 3a, as shown in **12**, because a *trans* fusion of the two five-membered rings introduces a large degree of bond strain. House and Blankley[7] have demonstrated that base-catalyzed alkylations of perhydroindan-1-ones at their ring junctures result in products containing 96% *cis*-fused systems. It is likewise concluded that C-methylation of the hexahydrofluorenone system **8** will result in the *cis* structure **10**; House and co-workers[8] have treated pure *cis*-**8** with sodium ethoxide and have obtained an equilibration mixture consisting of 15% *trans* and 85% *cis* material. Moreover, these workers found that *cis*-**8** reacted with acrylonitrile in the presence of benzyltrimethylammonium hydroxide to form a pure *cis* angularly cyanoethylated product. Evidence was also presented to indicate that bromination of *cis*-**8** yields a 9a-bromo compound in which the bromine is *cis* to the 4a hydrogen.

Examination of molecular models indicates that attack on the carbonyl group of **12** by an acetylide anion would be favored on the side of the molecule opposite that from which the cyclopentane ring protrudes; that is, the ethynyl group would enter *cis* to the 3a hydrogen to form **13**. Similar conclusions can



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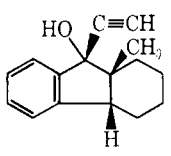

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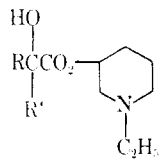
be drawn for **10**; the 9a angular methyl group is much less bulky than the cyclohexane ring, and the ethynyl anion will enter the molecule to give **14**.

The ethynyl carbinols **13**–**15** (Table I) were treated with neutral permanganate to yield the glycolic acids which were characterized as their methyl esters. The glycolic acid derived from **15** could be isolated only in amounts sufficient for characterization of the methyl ester, and further work on it was abandoned. Attempts to achieve a transesterification[9] between these methyl esters and N-methyl-3-piperidinol failed. However, the sodium salts of the glycolic acids (and of benzilic acid) reacted with N-methyl-3-piperidyl tosylate to form the desired ester products. Esterification of the glycolic acids by the sodium salt piperidyl tosylate method is less tedious and requires less reaction time than the transesterification; the sodium salts of the glycolic acids are easily prepared and require no extensive purification. The progress of the reaction can be followed by noting the separation of sodium tosylate from the reaction mixture.

Biel and co-workers,[10] *inter alia*, have reported that when N-ethyl-3-chloropiperidine is treated with glycolic acids in 2-propanol, a mixture of N-ethyl-3-piperidyl glycolate **23** and N-ethyl-2-pyrrolidylmethyl glycolate **24** is formed. That the products reported in the



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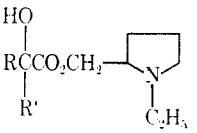

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present study (Table II) possess the piperidine structure **23** and not the pyrrolidylmethyl structure **24** was verified by their hydrolysis under strongly acidic conditions and isolation and identification of the amino alcohol product. This hydrolytic method was shown[10] *not* to induce ring expansion or contraction of the five- or of the six-membered ring amino alcohol systems. In the present study, the amino alcohol hydrolysis products in each instance exhibited ir spectra which were identical with a similar spectrum of an authentic sample of N-methyl-3-piperidinol. In addition, nmr spectra of the glycolate esters (Table II) in every case demonstrated a poorly resolved multiplet in the region δ 4.3–4.7 which integrated for one proton.

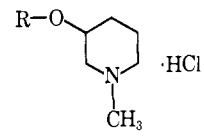
(7) H. O. House and C. J. Blankley, *J. Org. Chem.*, **32**, 1741 (1967).

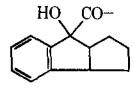
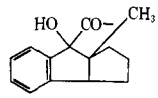
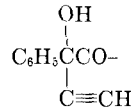
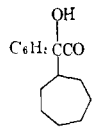
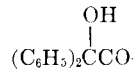
(8) H. O. House, V. Paragamian, R. S. Ro, and D. J. Wluka, *J. Am. Chem. Soc.*, **82**, 1457 (1960).

(9) J. G. Cannon, *J. Org. Chem.*, **25**, 959 (1960).

(10) J. H. Biel, L. G. Abood, W. K. Hoya, H. A. Leiser, P. A. Nolder, and E. F. Kluchesky, *ibid.*, **26**, 4096 (1961).

TABLE II
ESTERS OF N-METHYL-3-PIPERIDINOL



No.	R	Mp, °C	Yield, %[f]	Formula	Analyses
21		201[a]	13	$C_{19}H_{26}ClNO_3$	C, H, Cl, N
22		215–216[b]	9	$C_{20}H_{28}ClNO_3$	C, H, Cl, N
1		186[c]	30	$C_{16}H_{20}ClNO_3$	C, H, Cl, N
2		220–221[a]	60	$C_{21}H_{32}ClNO_3$	C, H, N; Cl[g]
		221–222[d,e]	35		

[a] From Me_2CO. [b] From Me_2CO–Et_2O. [c] From Me_2CO–MeOH. [d] From *i*-PrOH–Et_2O. [e] J. H. Biel, E. P. Sprengler, H. A. Leiser, J. Horner, A. Drukker, and H. L. Friedman, *J. Am. Chem. Soc.*, **77**, 2250 (1955), reported mp 221–223°. [f] Yields were calculated from the corresponding glycolic acid. [g] Cl: calcd, 9.32; found, 9.74.

A spectrum of an authentic sample of N-methyl-3-piperidyl 2,2′-dichlorobenzilate[9] (prepared by transesterification) contained a poorly resolved signal centered at δ 4.25 which integrated for one proton. These signals are attributed to the C-3 proton of N-methyl-3-piperidinol.

Pharmacology. Methods.—The pharmacological procedures for evaluating anticholinergic and central nervous system action are described elsewhere.[11,12] Behavioral performance was evaluated by measuring the effect of the drugs on motor activity (rat) and swim maze performance [mouse and so-called "peek" test (mouse)]. The correlation of these tests with the psychotomimetic activity in man is also discussed elsewhere.[11,12]

Discussion (See Table III).—The observation that the hexahydrocyclopent[*a*]indene ester **21** exhibited high anticholinergic but low psychotomimetic potency corroborates the hypothesis that coplanarity of the ring structures of the acid moiety is required for optimal central nervous system (CNS) action. Since this compound retains high (peripheral) anticholnergic activity, it would appear that the drug receptors in the central nervous system, either at the level of the blood–brain barrier or synapses, are different from those at peripheral sites. Introduction of the 9a-methyl group (**22**) in this ring structure significantly diminished anticholinergic potency and abolished CNS efficacy. It is also conceivable that a rigid heterocyclic moiety may hinder the attachment of the molecule to a lipophilic portion of the biological receptor. The marked CNS activity of the cycloheptylphenylglycolate ester **2** is consistent with the observation that Catalin models indicate that the cycloheptane and the benzene rings can exist in an over-all coplanar conformation. The extended duration of mydriatic action of **21** and of **2** (Table III) is striking and noteworthy.

(11) L. G. Abood and J. H. Biel, *Intern. Rev. Neurobiol.*, **4**, 217 (1962).
(12) N. W. Gabel and L. G. Abood, *J. Med. Chem.*, **8**, 616 (1965).

Experimental Section[13]

1,2,3,3a,8,8a-Hexahydrocyclopent[*a*]inden-8-one (**7**) was prepared by the method of Baker and Jones,[14] bp 110° (0.1 mm), lit.[14] bp 145° (12 mm), $n^{25}D$ 1.5714.

Ethyl *trans*-2-Phenylcyclohex-4-ene-1-carboxylate (**16**).—A mixture of 30 g (0.17 mole) of ethyl *trans*-cinnamate, 9.21 g (0.17 mole) of butadiene, and 0.5 g of hydroquinone was shaken in a reaction autoclave at 175° for 12 hr. The resulting clear solution was distilled and the fraction boiling at 100–105° (0.06 mm) was collected, yield 24 g (82%), $n^{20}D$ 1.5280. *Anal.* ($C_{15}H_{18}O_2$) C, H.

***trans*-2-Phenylcyclohex-4-ene-1-carboxylic Acid** (**17**).—A solution of 48 g (0.21 mole) of **16**, 60 g of NaOH, 300 ml of H_2O, and 350 ml of EtOH was vigorously refluxed on a steam bath for 6 hr. The volume was reduced to 100 ml and the remaining liquid was acidified with concentrated HCl. The resulting precipitate was collected on a filter, then dissolved in 10% $NaHCO_3$; this solution was treated with charcoal, filtered, and reacidified with concentrated HCl to yield a solid which was recrystallized from Skelley B and dried under vacuum at room temperature to produce 36 g (79%) of material, mp 101–102°, lit.[15] mp 99–101°.

***trans*-2-Phenylcyclohexanecarboxylic acid** (**18**) was prepared from **17** by the method of Klein and Levin;[15] mp 109°, lit.[15] mp 108°.

(13) All melting points are corrected and were determined on a Fisher-Johns apparatus, unless otherwise specified. Analyses were by Huffman Microanalytical Laboratory, Wheatridge, Colo., Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and Crobaugh Laboratories, Cleveland, Ohio.. Nmr spectra were determined on a Varian Associates A-60 instrument. Where analyses are indicated only by symbols of the elements, the analytical results obtained for those elements were within ±0.4% of the theoretical values.
(14) W. Baker and P. G. Jones, *J. Chem. Soc.*, 787 (1951).
(15) J. Klein and G. Levin, *J. Am. Chem. Soc.*, **80**, 1707 (1958).

TABLE III
BEHAVIORAL AND ANTICHOLINERGIC EFFECTS OF N-METHYL-3-PIPERIDINOL GLYCOLIC ACID ESTERS

				Cholinergic blockage			
					Mydriasis[d]		
Compd	Activity cage[a]	Swim maze[b]	Peek test[c]	Ileum ED_{50}[d]	Molar concn	Tone hr	BDI[f]
21	4.0	3.8	2.8	5×10^{-6}	3×10^{-2}	8+	10.6
22	2.5	3.5	2.6	1×10^{-5}	6×10^{-2}	6.5	8.6
1	3.5	3.5	2.7	1×10^{-5}	5×10^{-4}	1.5	9.7
2	4.4	4.6	3.0	1×10^{-7}	1×10^{-3}	8+	12.0
3-PB[g]	4.5	4.5	2.9	2×10^{-7}	3×10^{-5}	6	11.9
Saline	0.6	2.6	2.5	...	...	...	5.7

[a] Activity cage values (rats) are expressed as oscillations per 0.03 min. [b] Swim maze values (mice) are in terms of errors on the fourth trial. [c] Peek test values (mice) are in terms of total number of peeks. The dose in all tests was 1 mg/kg ip. [d] Molar concentration of drug to produce 50% inhibition of acetylcholine-induced spasms of isolated rabbit ileum. [e] Molar concentration of drug to produce complete mydriasis when 0.05 ml is applied directly to rat's eye. [f] Behavioral disturbance index (an arithmetical sum of activity cage, swim maze, and peek test values). [g] N-Methyl-3-piperidyl benzilate (see ref 10 and 11).

cis-**1,2,3,4,4a,9a-Hexahydrofluoren-9-one** (**18**) was prepared from **18** by the method of Cook and Hewitt;[16] mp 40–41°, bp 85–98° (0.05 mm), lit.[16] bp 130–132° (1.0 mm).

8a-Methyl-1,2,3,3a,8,8a-hexahydrocyclopent[*a*]inden-8-one (**12**). **Method A.**—The method of Peak and Robinson[17] was employed. Compound **7** (75 g, 0.436 mole) was added with stirring to a solution of 30 g (0.77 g-atom) of K in 500 ml of *t*-BuOH, after which 70 g (2.73 moles) of MeI was added dropwise over 1 hr, followed by refluxing for 1 hr. The KI precipitate was removed by filtration and the solvent was removed under reduced pressure. The residual liquid was washed with H_2O and dried ($MgSO_4$); nmr (CCl_4), δ 1.278 (s, 1.5). Gas chromatographic analysis indicated a mixture of two components, in approximately equal amounts; one had a retention time identical with that of starting material **7**, and the other component was assumed to be the methylated product. The methylation procedure was repeated on this mixture three times; after each reaction, gas chromatograms indicated an increase in the amount of methylated product at the expense of starting material. Finally, no starting material **7** could be detected; 45.6 g (56%) of methylated product **12** was obtained; bp 110° (2.25 mm), lit.[5] bp 138–141° (8.0 mm); $n^{25}D$ 1.5477; nmr (CCl_4), δ 1.278 (s, 3). *Anal.* ($C_{13}H_{14}O$) C, H.

Method B.—Potassium (2.3 g, 0.059 g-atom) was dissolved in a solution of 10 g (0.058 mole) of **7** in 50 ml of C_6H_6. MeI (3.42 g, 0.024 mole) was added in one portion to the wine red solution, and 20 g (0.14 mole) of additional MeI was added in small amounts over 1 hr. The reaction mixture was filtered, the filtrate was washed with H_2O and dried ($MgSO_4$), and the solvent was removed under reduced pressure, leaving 8 g of liquid. Gas chromatographic analysis of this material indicated a composition of 45% of methylated product **12** and 55% of starting material **7**. The methylation reaction was repeated on this mixture; gas chromatographic analysis of the crude reaction product of the second methylation indicated the presence of **12** and of *two* other components, neither of which was isolated or identified.

cis-**9a-Methyl-1,2,3,4,4a,9a-hexahydrofluoren-9-one** (**10**) was prepared from **8** in a manner analogous to method A for **12**. In this case, the starting ketone **8** required only a single treatment with K-*t*-OBu and MeI; yield 46.5 g (80%); bp 90° (0.05 mm), lit.[6] bp 145–147° (10 mm); $n^{25}D$ 1.5540; nmr (CCl_4), δ 1.248 (s, 3). *Anal.* ($C_{14}H_{16}O$) C, H.

Ethynyl alcohols were prepared by a procedure based upon that of Beumel and Harris.[18] Purified, dried acetylene was passed for 0.5 hr into a suspension of 0.18 mole of lithium acetylide-ethylenediamine (Foote Mineral Co.) in 100 ml of THF. The appropriate ketone (0.087 mole) in 50 ml of THF was added dropwise and the reaction mixture was stirred at room temperature for 3 hr. H_2O (100 ml) was added slowly; the aqueous layer was separated and washed twice with ether which was added to the organic layer. The combined organic layers were evaporated under reduced pressure; an oil remained which was crystallized by dissolving it in Skelley B and adding a few drops of MeOH (see Table I); ir ($CHCl_3$), 3575 (OH) and 3300 cm^{-1} (C≡C).

The mercury complexes of two of the ethynyl alcohols were prepared by treating them with excess Na_2HgI_4 reagent.[19] Upon addition of a small amount of H_2O, the Hg complex precipitated and could be recrystallized (C_6H_6–Skelley B) (see Table I).

Glycolic Acids.—$KMnO_4$ (86 g, 0.54 mole) in 1 l. of H_2O was added dropwise over 22 hr with stirring to a solution of 0.20 mole of the appropriate ethynyl alcohol in 150 ml of ether. The reaction mixture was maintained at 0–5° and stirring was continued for 2 hr after addition of the permanganate. It was passed through a centrifuge-type filter until clear, and the filtrate was extracted with ether. The filtrate was next acidified with 10% HCl and was extracted three times with ether. These combined extracts were dried ($MgSO_4$) and filtered, and the ether was removed to afford an oil which could be crystallized and partially purified by dissolving it in 5% $NaHCO_3$, extracting the solution with ether, acidifying with 10% HCl, extracting with ether, and removing this ether to yield a crystalline solid.

Methyl esters of glycolic acids were prepared from the acids with CH_2N_2 (see Table I).

Sodium Salts of Glycolic Acids.—The solid acid was treated with 5% aqueous $NaHCO_3$; H_2O was removed under reduced pressure, and the residual solid was dissolved in anhydrous MeOH. The insoluble excess $NaHCO_3$ was removed by filtration and the organic salt was crystallized by addition of dry ether to the filtrate.

N-Methyl-3-piperidyl Tosylate Hydrochloride (**19**). Tosyl chloride (85.5 g, 0.45 mole) in 200 ml of pyridine was added with stirring to 26.1 g (0.227 mole) of N-methyl-3-piperidinol (Aldrich Chemical Co.) in 100 ml of pyridine, at such a rate that the temperature remained below 50°. The resulting mixture was permitted to stand overnight, then the pyridine was removed under reduced pressure. The residual red oil was cooled and anhydrous acetone was added; a white solid separated which was collected on a filter and recrystallized from MeOH–ether to afford 41.5 g (60%) of white crystals, mp 146–148°. *Anal.* ($C_{13}H_{20}ClNO_3S$) C, H, N.

N-Methyl-3-piperidyl tosylate (**20**) was obtained by treating 1.12 g (0.037 mole) of **19** with excess 5% $NaHCO_3$, extracting with ether, drying the ethereal extract ($MgSO_4$), and removing the ether. The solid residue (0.9 g, 91%) showed mp 44–45°.

N-Methyl-3-piperidyl Esters of Glycolic Acids.—A mixture of 0.01 mole of the sodium salt of the appropriate glycolic acid and 2.69 g (0.01 mole) of **20** in 75 ml of anhydrous acetone was stirred at room temperature for 10 hr. The white precipitate which formed during the course of the reaction was removed by filtration, and the solvent was removed from the filtrate under reduced pressure. The oily residue was extracted repeatedly with ether; the combined extracts were washed (H_2O) and dried ($MgSO_4$), and the ether was removed on a steam bath, leaving a semisolid residue. (In the case of sodium benzilate, an ir spectrum of this semisolid was identical with one obtained from an authentic sample of N-methyl-3-piperidyl benzilate.) The semisolid was dissolved in dry ether and was treated with ethereal HCl; the solid which separated was recrystallized repeatedly (see Table II). Thin layer chromatographic analysis indicated in all instances the presence of an single component in the products of

(16) J. W. Cook and C. L. Hewitt, *J. Chem. Soc.*, 62 (1936).
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(19) J. R. Johnson and W. L. McEwen, *J. Am. Chem. Soc.*, **48**, 469 (1926).

the esterification reactions. Nmr spectra were recorded on the HCl salts in dimethyl-d_6 sulfoxide.

Hydrolysis of N-Methyl-3-Piperidyl Esters of Glycolic Acids.—The method of Biel and co-workers[10] was employed. A 0.45-g sample of the N-methyl-3-piperidyl glycolate HCl (**1**, **2**, **21**, or **22**, Table II) was heated vigorously for 1 hr in 30 ml of 33% H_2SO_4. The cooled solution was decanted from resinous material and was extracted three times with ether. The aqueous solution was cooled in an ice bath, made strongly alkaline with NaOH pellets, then was extracted repeatedly with ether. The combined ethereal extracts were dried (Na_2SO_4), and the ir spectrum was recorded. In each instance, the spectrum was superimposable upon a similar spectrum of an authentic sample of N-methyl-3-piperidinol.

Chemistry and Pharmacology of a Series of Substituted 4H-Pyrazino[1,2-*a*]pyrimidin-4-ones

DONALD L. TREPANIER, L. W. RAMPY, KENNETH L. SHRIVER,

Chemistry Research Department

JOHN N. EBLE, AND PHILIP J. SHEA

Pharmacology Department, Human Health Research and Development Center, The Dow Chemical Company, Zionsville, Indiana

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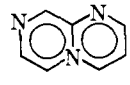
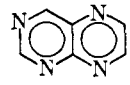
A series of 3-phenyl-2-(tertiary aminoalkoxy)-4H-pyrazino[1,2-*a*]pyrimidinones obtained by condensing ethyl phenylmalonate with aminopyrazine followed by base-catalyzed O-tertiary-amino alkylation of the resulting 2-hydroxy-3-phenyl-4H-pyrazino[1,2-*a*]pyrimidin-4-one was screened for CNS activity in mice. None showed significant activity in the maximal electroshock, oxotremorine, strychnine lethality, pentylenetetrazole seizure threshold, or *d*-amphetamine aggregate toxicity tests. Some potentiated the effect of hexobarbital and *d*-amphetamine in mice and antagonized the effect of reserpine.

A search of the chemical literature revealed that the pyrazino[1,2-*a*]pyrimidine system has not been reported. In fact, the only pyrazinopyrimidine system reported is that found in the pteridines, the pyrimido[4,5-*b*]pyrazine heterocycle. This prompted us to undertake a synthesis and pharmacological testing study in this area. This paper reports the results of this study.



pyrazino[1,2-*a*]pyrimidine



pyrimido[4,5-*b*]pyrazine

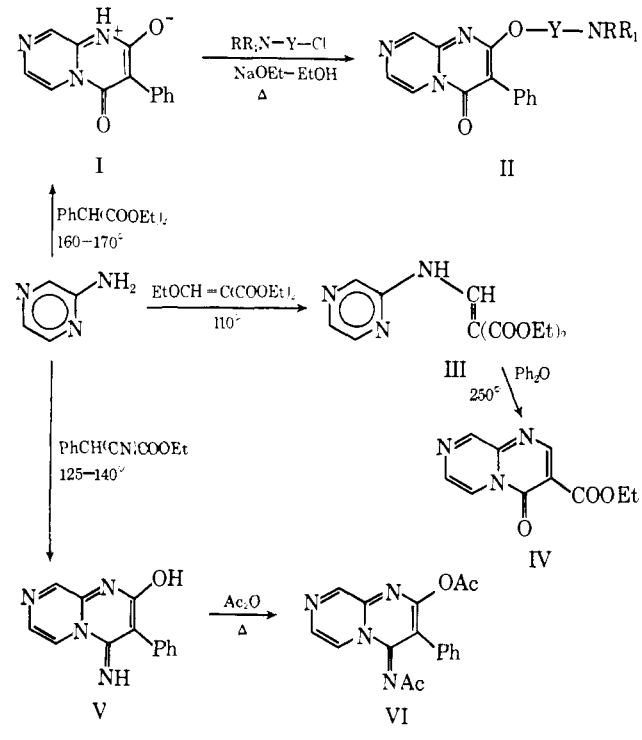
Because our primary interest was the uncovering of new structures with central nervous system activity, derivatives of the pyrazino[1,2-*a*]pyrimidine heterocycle that contained a phenyl or substituted phenyl in the 3 position and a tertiary aminoalkoxy chain in the 2 position were synthesized and evaluated for CNS activity. This type of derivative was selected for synthesis because it contains a type of phenethylamine moiety and a choline or choline-like side chain which increases the likelihood it will affect the CNS neurotransmitters, norepinephrine and acetylcholine.

The desired 3-phenyl-2-(tertiary aminoalkoxy)pyrazino[1,2-*a*]pyrimidin-4-ones (II) were obtained by condensing ethyl phenylmalonate with aminopyrazine followed by base-catalyzed O-alkylation of the resulting 2-hydroxy-3-phenyl-4H-pyrazino[1,2-*a*]pyrimidin-4-one (I) (Scheme I).

In order to obtain more diverse structural modifications pyrazinopyrimidinone I was O-alkylated with α-chloro esters and chloracetonitrile, and aminopyrazine was condensed with diethyl ethoxymethylenemalonate and diethyl phenylcyanoacetate.

When aminopyrazine was allowed to react with diethyl ethoxymethylenemalonate neat at 110° a 63% yield of diethyl pyrazinylaminomethylenemalonate

SCHEME I



(III) was obtained. That the *exo*-amino nitrogen and not one of the ring nitrogens was alkylated was indicated by the pmr spectrum of III. The vinyl proton and the D_2O exchangeable proton on the *exo* nitrogen appeared as doublets (J = 12.5 cps) at 543 and 672 cps, respectively. The pmr spectrum of the alternative structure, alkylation of a ring nitrogen, would not show a vinyl proton coupled with an exchangeable NH proton. Ring closure of III to 3-carboethoxy-4H-pyrazino[1,2-*a*]pyrimidin-4-one (IV) was accomplished in 89% yield by heating III at 250° in Dowtherm.