[CONTRIBUTION FROM THE RESEARCH DIVISION OF LAKESIDE LABORATORIES, INC. AND THE UNIVERSITY OF ILLINOIS MEDICAL COLLEGE]

Central Stimulants. II. Cholinergic Blocking Agents[1]

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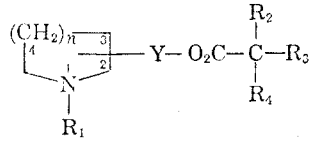
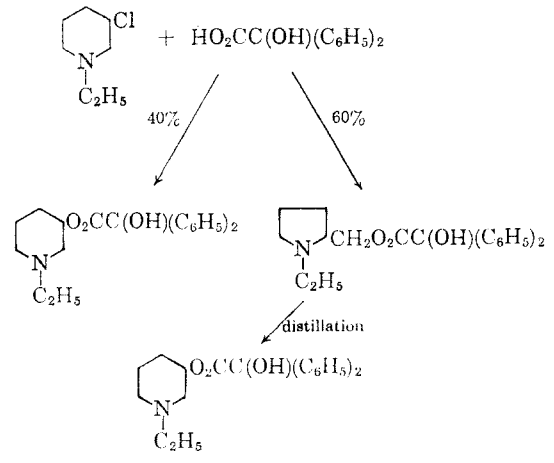
The initial finding that certain disubstituted glycolates of 3-hydroxypiperidine could elicit potent psychotomimetic and antidepressant effects in man suggested a possible relationship between cholinergic blockade and central nervous system stimulatory properties. To investigate this hypothesis, a structural variety of esters of the hydroxypiperidines, hydroxypyrrolidines and hydroxymethylpyrrolidines was synthesized. The following aspects of this investigation will be discussed: (1) The ring contraction obtained during the reaction of the 3-halopiperidines with the free acid, (2) the thermal ring expansion during the distillation of the basic esters, (3) the structure-activity relationships with regard to (a) central nervous system stimulation, (b) anticholinergic effects and (c) the correlation of psychopharmacologic action with cholinergic blockade, (4) the use of these psychotogenic drugs as possible tools in the development of potential antagonists. At present, the conclusion appears warranted that potent anticholinergic properties are a pharmacologic prerequisite for the characteristic central nervous system effects evoked by this group of compounds.

The potent psychotomimetic and central stimulatory properties exhibited by a group of disubstituted glycolate esters of *N*-methyl and *N*-ethyl-3-hydroxypiperidine[2] which were also potent cholinergic blocking agents[3] suggested the possible involvement of acetylcholine as a neurotransmitter substance in the control of lower brain functions.

In order to investigate this hypothesis further, it became necessary to synthesize a large variety of related compounds with a view toward establishing a possible relationship between central excitation and anticholinergic activity. The scope of the structural variants is delineated by the generic formula shown below:



where R_1 is H, alkyl, alkenyl, amino, aminoalkyl, hydroxyalkyl, aralkyl, aralkenyl; R_2 is H, OH, alkyl, alkoxy; R_3 is phenyl, substituted phenyl; R_4 is phenyl, substituted phenyl, cycloalkyl, thienyl; Y is a chemical bond or a lower straight or branched alkylene chain; n is 1 or 2. The esters were prepared by two routes: (1) reaction of the *N*-substituted 3-chloropiperidine with the free acid; (2) ester interchange of the amino alcohol with the methyl esters. While the ring contraction during the reaction of *N*-ethyl-3-chloropiperidine with amines has been described by Reitsema[4] and confirmed in our laboratories,[5] no such instance had been reported for the reaction of the 3-chloropiperidines with the free acids. In fact, our early studies had proved conclusively that no ring contraction had taken place[6] during the esterification reaction. In these studies, the basic piperidyl esters had always been isolated by a high vacuum distillation. When the distillation step was omitted and the crude esters converted directly to their salts, it was found that the major products were the "ring-contracted" 2-pyrrolidylmethyl esters. In the case of the benzilate esters, the ratio of 2-pyrrolidylmethyl *vs.* 3-piperidyl benzilates was 6:4, and in the case of the phenylcyclopentylglycolates, 7:3, respectively. When the ester salts were converted to the free bases and the latter subjected to a high vacuum distillation, a ring expansion to the 3-piperidyl esters occurred in almost quantitative yield (the ring-expanded isomer was the sole product isolated). No rearrangement occurred during the hydrolysis of the esters to the alcohols:



(1) Presented in part during the Frederick F. Blicke Symposium at the 139th Meeting of the American Chemical Society, September, 1960, before the Division of Medicinal Chemistry.

(2) L. G. Abood, A. M. Ostfeld, and J. H. Biel, *Proc. Soc. Exptl. Biol. Med.*, 97, 483–486 (1958).

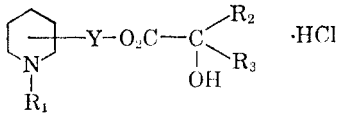
(3) J. H. Biel, E. P. Sprengeler, H. A. Leiser, J. Horner, A. Drukker, H. L. Friedman, *J. Am. Chem. Soc.*, 77, 2250 (1955).

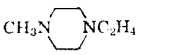
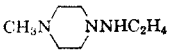
(4) P. R. Reitsema, *J. Am. Chem. Soc.*, 71, 2041 (1949).

(5) J. H. Biel, W. K. Hoya, and H. A. Leiser, *J. Am. Chem. Soc.*, 81, 2527 (1959).

(6) J. H. Biel, H. L. Friedman, H. A. Leiser, and E. P. Sprengeler, *J. Am. Chem. Soc.*, 74, 1485 (1952).

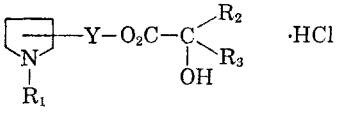
TABLE I



R_1	R_2	R_3	Ring Pos'n	Y	Yield, %	M.P.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
C_2H_5	C_6H_5	C_5H_9	3	—	—	212–213	$C_{20}H_{30}ClNO_3$	3.81	—	9.65	—
CH_3	C_6H_{11}	C_6H_5	3	—	76.0	222	$C_{20}H_{30}ClNO_3$	3.81	3.82	9.65	9.75
H	C_6H_5	C_6H_5	3	—	96.5	178–180	$C_{19}H_{22}ClNO_3$	4.03	4.01	10.20	10.27
$C_6H_5CH_2$	C_6H_5	C_6H_5	3	—	75.0	222–223	$C_{26}H_{28}ClNO_3$	3.20	3.35	8.11	7.88
$(CH_3)_2NC_2H_4$	C_6H_5	C_6H_5	3	—	68.0	237–238	$C_{23}H_{32}Cl_2N_2O_3$	6.15	6.14	15.57	15.61
	C_6H_5	C_6H_5	3	—	53.0	257	$C_{26}H_{38}Cl_3N_3O_3$	7.68	7.62	19.45	19.30
$C_6H_5CH_2OC_2H_4$	C_6H_5	C_6H_5	3	—	69.0	172	$C_{28}H_{32}ClNO_4$	2.90	2.91	7.36	7.30
$C_6H_5CH_2$	C_6H_5	C_6H_5	2	CH_2	67.2	211	$C_{27}H_{30}ClNO_3$	3.10	3.12	7.84	7.83
HOC_2H_4	C_6H_5	C_6H_5	3	—	98.5	152–52.5	$C_{21}H_{26}ClNO_4$	3.57	3.57	9.06	8.99
H	C_6H_5	C_6H_5	2	CH_2	81.0	199–200	$C_{20}H_{24}ClNO_3$	3.87	3.85	9.80	9.76
CH_3	C_6H_5	C_6H_5	2	CH_2	44.3	230	$C_{21}H_{26}ClNO_3$	3.72	3.66	9.43	9.58
$C_6H_5CH_2$	C_6H_5	C_6H_5	4	—	78.2	194–195	$C_{26}H_{28}ClNO_3$	3.20	3.19	8.11	8.01
CH_3	C_6H_5	C_6H_5	2	CH CH_2	31.4	230	$C_{22}H_{23}ClNO_3$	3.59	3.59	9.09	9.04
[a]	C_6H_5	C_6H_5	3	CH_2	29.2	189	$C_{20}H_{18}ClNO_4$	3.98	3.99	9.96	10.01
H	C_6H_5	C_6H_5	4	—	88.0	180–182	$C_{19}H_{22}ClNO_3$	4.03	3.95	10.20	10.00
CH_3	C_5H_9	C_6H_5	3	—	58.7	209–210	$C_{19}H_{28}ClNO_3$	3.95	3.90	10.01	10.18
CH_3[b]	C_6H_5	C_6H_5	3	—	71.0	216–217	$C_{21}H_{26}ClNO_2$	3.89	3.90	9.85	9.89
	C_6H_5	C_6H_5	3	—	77.0	237–239	$C_{26}H_{39}Cl_3N_4O_3$	9.97	10.10	18.93	18.99
C_2H_5	C_6H_5	C_5H_9	4	—	43.5	220–221	$C_{20}H_{30}ClNO_3$	3.81	3.96	9.65	9.97
CH_3	C_6H_5	C_6H_5	4	—		213–214	$C_{20}H_{24}ClNO_3$	3.88	3.89	9.84	9.78
CH_3	C_6H_5	C_5H_9	2	C_2H_4	26.7	145–147	$C_{21}H_{32}ClNO_3$	3.67	3.70	9.28	9.30
CH_3NH	C_6H_5	C_6H_5	3	—	30.0	158–160	$C_{34}H_{28}N_2O_7$	3.06	3.01		
CH_3	C_6H_5	C_6H_5	4	—	53.0	215–216	$C_{20}H_{24}ClNO_3$	3.87	4.01	9.79	10.02
H[c]	C_6H_5	C_6H_5	3	—	56.0	171–172	$C_{19}H_{22}ClNO_2$	4.22	4.36	10.68	10.75

[a] 3-Pyridyl instead of *N*-alkyl-3-piperidyl. [b] CH_3 in place of OH in ester moiety. [c] H in place of OH in ester moiety.

TABLE II



R_1	R_2	R_3	Ring Pos'n	Y	Yield, %	M.P.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
C_2H_5	C_6H_5	C_5H_9	2	CH_2	30.0	186	$C_{20}H_{30}ClNO_3$	3.81	3.83	9.66	9.77
CH_3[a]	C_6H_5	C_5H_9	3	—	31.0	169–170	$C_{18}H_{26}ClNO_3$	4.12	4.20	10.43	10.45
C_2H_5[a]	C_6H_5	C_5H_9	3	—	42.0	165–166	$C_{19}H_{28}ClNO_3$	3.95	3.95	10.01	10.12

[a] Amino alcohols prepared by method described by C. D. Lunsford, J. W. Ward, A. J. Pallotta, T. W. Tusing, E. K. Rose, and R. S. Murphy; *J. Med. and Pharm. Chem.*, Vol. I, No. 1, page 73 (1959).

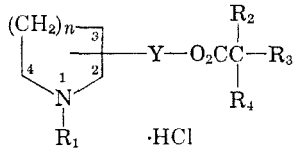
The isomer ratios were established by infrared spectroscopy of the hydrolyzed basic alcohols.

A ring expansion of *N*-ethyl-2-pyrrolidylmethyl-chloride hydrochloride to *N*-ethyl-3-chloropiperidine hydrochloride has been reported previously by Fuson and Zirkle.[7] Additional evidence for the lability of the *N*-alkylpiperidyl and 2-pyrrolidylmethyl systems has been presented recently by Paul and Tchelitcheff.[8] The esters were evaluated in the form of their acid addition or quaternary ammonium salts for their anticholinergic effects in the isolated, perfused guinea pig ileum and for their central nervous system stimulant properties by the modified jiggle cage technique. The comparative pharmacologic activities are recorded in Table III. Anticholinergic potency is expressed as the dilution of the drug in parts per million capable of inhibiting acetylcholine-induced spasms by 50% (ED_{50}). Central nervous system activity is expressed as the threshold dose of the drug which

(7) R. C. Fuson and C. L. Zirkle, *J. Am. Chem. Soc.*, 70, 2760 (1948).

(8) R. Paul and S. Tchelitcheff, *Bull. Soc. Chim.*, 1958, 736.

TABLE III



No.	R_1	R_2	R_3	R_4	n	Ring Pos'n	Y	CNS Stim. Mg/Kg (s.c.)	ED_{50} *vs.* AcCh 1:1 × 10^6
1	H	OH	C_6H_5	C_6H_5	2	3	—	5.0	158
2	H	OH	C_6H_5	C_6H_5	2	2	CH_2	20.0	14
3	CH_3	OH	C_6H_5	C_6H_5	2	3	—	0.2	300
4	C_2H_5	OH	C_6H_5	C_6H_5	2	3	—	—	200
5	C_2H_5	H	C_6H_5	C_6H_5	2	3	—	None	4
6	CH_3	CH_3	C_6H_5	C_6H_5	2	3	—	None	250
7	CH_3	OH	C_6H_5	C_6H_5	2	2	CH_2	0.5	139
8	CH_3	OH	C_6H_5	C_6H_5	1	2	$CHCH_3$	20.0	—
9	CH_3[a]	OH	C_6H_5	C_5H_9	2	3	—	0.05	476
10	CH_3	OH	C_6H_5	C_6H_5	1	3	—	0.05	200
11	C_2H_5	OH	C_6H_5	C_5H_9	1	2	CH_2	0.2	348
12	CH_3	OH	C_6H_5	C_5H_9	2	2	C_2H_4	0.5	260
13	C_2H_5	OH	C_6H_5	C_5H_9	1	3	—	0.05	435
14	CH_3	OH	C_6H_5	C_6H_5	2	4		0.2	835
15	C_2H_5	OH	C_6H_5	C_5H_9	2	3		0.05	375
15a	High melting diastereoisomer of 15							5.0	20
16	CH_3	OH	C_6H_5	C_4H_3S	2	3		0.2	1,000
17	CH_3	OH	C_6H_5	C_6H_{11}	2	3		0.2	392
18	$CH_2CH{=}CH_2$[a]	OH	C_6H_5	C_6H_5	2	3		20.0	303
19	$C_6H_5C_2H_4$[a]	OH	C_6H_5	C_6H_5	2	3		None	313
20	$C_6H_5CH_2$	OH	C_6H_5	C_6H_5	2	3		None	0.2
21	4° Salt of 20[a]							None	2.3
22	$C_6H_5CH{=}CHCH_2$[a]	OH	C_6H_5	C_6H_5	2	3		None	2.7
23	4° Salt of 22[a]				2	3		None	57.0
24	NCH_3	OH	C_6H_5	C_6H_5	2	3	—	10.0	81.0
25	HOC_2H_4	OH	C_6H_5	C_6H_5	2	3	—	20.0	21.0
26	$(CH_3)_2NC_2H_4$	OH	C_6H_5	C_6H_5	2	3	—	None	24.0
27	$(CH_3)_2N(CH_2)_3$[a]	OH	C_6H_5	C_6H_5	2	3	—	20.0	1.0
28	$C_5H_{10}NC_2H_4$[a]	OH	C_6H_5	C_6H_5	2	3	—	20.0	8.0
29	$C_4H_8NOC_2H_4$[a]	OH	C_6H_5	C_6H_5	2	3	—	20.0	3.0
30	$CH_3NC_4H_8NC_2H_4$	OH	C_6H_5	C_6H_5	2	3	—	None	182.0
31	$CH_3NC_4H_8N(CH_2)_3$[a]	OH	C_6H_5	C_6H_5	2	3	—	None	14
32	CH_3[a]	OH	C_6H_5	1-OHC_6H_{10}	2	3	—	1.0	40
33	CH_3[a]	OH	C_6H_5	1-OHC_5H_8	2	3	—	0.5	111
34	CH_3[a]	H	C_6H_5	1-OHC_5H_8	2	3	—	0.2	526
35	4° Salt of 34[a]							None	455
36	CH_3[a]	H		1-OHC_6H_{10}	2	3	—	0.2	476
								1.2	450

[a] Atropine supplied for our structure-activity studies by Professor F. F. Blicke, College of Pharmacy, University of Michigan, Ann Arbor, Mich. The chemistry of these compounds will be described in one of Professor Blicke's forthcoming publications.

produced an increase in spontaneous motor activity in rats.

The data in Table III allow the following conclusions regarding structure-activity relationships: (1) R_1 should be a lower alkyl group for potent central nervous system stimulant effects (*viz.* compounds, 3, 7, 9–17, 33, 34, 36). Substituents such as hydrogen (Nos. 1 and 2), alkenyl (No. 18), hydroxyalkyl (No. 25), aralkyl (Nos. 19, 20, 22), aralkenyl (No. 22), methylamino (No. 24), and aminoalkyl (Nos. 26–31 incl.) either destroy the central stimulant activity possessed by the parent compounds or greatly diminish it without necessarily affecting anticholinergic potency (*viz.* compounds 18, 19, 30). Since *N*-allylnormorphine is a potent antagonist of morphine, the *N*-allyl derivative (No. 18) was tested as a possible antagonist to such potent central nervous system stimulants as No. 3. It was found that it would indeed greatly diminish or partially reverse the central nervous system effects elicited by the corresponding *N*-ethyl derivative (No. 3) in the rat. (2) R_2 must be a hydroxyl group; compounds having a hydrogen (No. 5), an isosteric methyl (No. 6) or a methoxy group for R_2[9] are devoid of central stimulant properties. However, compound 6 is still a very potent anticholinergic agent. (3) R_3 should be an unsubstituted phenyl group for optimum central nervous

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

system stimulant effects. A series of substituted phenyl derivatives prepared by Cannon[9] and tested by one of us (L. G. Abood), proved to be devoid of any central action. Substituents such as methyl, methoxy, dimethoxy, methylenedioxy and chloro were placed in various positions of the phenyl rings. (4) R_4 should be either phenyl, thienyl, cycloalkyl or 1-hydroxycycloalkyl for potent central nervous system and anticholinergic effects. The presence of two hydroxyl groups (Nos. 32 and 33 *vs.* 34 and 36) greatly diminished both types of pharmacologic activity. (5) Where Y was a chemical bond, optimum pharmacologic effects were obtained. The insertion of an alkylene or branched alkylene group between the ester moiety and the heterocyclic ring (Nos. 2, 7, 8, 11, 12) decreased or abolished activity. The 3-piperidyl esters yielded compounds with the most consistent central nervous system properties. Toxicity was greatly increased by going from the three to the four position of the piperidine ring. (6) Only those compounds with potent anticholinergic properties were also effective central nervous system stimulants. However, not every potent anticholinergic was necessarily an effective central nervous system drug.

Two of the piperidyl esters, *N*-ethyl-3-piperidyl benzilate and *N*-ethyl-3-piperidyl phenylcyclopentylglycolate, were tritiated and their distribution and excretion studied in rats. Over 95% of either drug was excreted in the urine after two hours. Only 0.1% of total drug was found in the central nervous system with the largest concentration in the caudate nucleus and hypothalamus.[10] Hence, these drugs exert their central stimulant and psychotogenic effects at microgram dosages.

Clinically, one of the compounds, JB-329 (*N*-ethyl-3-piperidyl phenylcyclopentylglycolate), has been used successfully as an antidepressant agent. Reversal of the depressive episode will occur in 50–70% of the cases treated after one or two 15-mg. administrations of the drug. Those patients experiencing the most intense psychotic episode will also respond best to the antidepressant action of this compound.[11,12]

In conclusion, it may be stated that we have presented evidence for a possible role of acetylcholine in the regulation of lower brain functions which are concerned with emotion, mood and behavior. This evidence is based on the following findings that (1) a series of potent cholinergic blocking agents produced a profound stimulation of the central nervous system, (2) the anticholinergic properties were an absolute requirement for this type of activity, (3) a reversal of all of the central effects could be brought about by the infusion of a cholinesterase inhibitor, 9-amino-1,2,3-4-tetrahydroacridine[13] which prevents the metabolic destruction of acetylcholine and allows it to accumulate in the body, (4) in a variety of mentally depressed patients remissions were obtained by one or two administrations of compound No. 15. From this it would appear that acetylcholine may play the same counterpart to norepinephrine in the brain as it does in the autonomic nervous system. This view is lent further support by the fact that these compounds exert little effect on any of the other known enzyme systems in the body.[14] Acetylcholine or an acetylcholine-like substance may therefore be the chemical mediator of the central depressant functions of the brain, and the development of central cholinergic blocking agents would offer a novel therapeutic approach to the treatment of mental depression in the same way as central adrenergic blocking drugs have in the therapy of combative behavior and the control of anxiety states. Furthermore, the discovery of potent psychotomimetic agents which precipitate a temporary psychosis in man indistinguishable from the true disease[12] has furnished valuable tools for the development of anti-psychotic drugs several of which are now undergoing clinical trial.

EXPERIMENTAL[15]

Assay for the isomer ratio of N-ethyl-3-piperidyl phenylcyclopentylglycolate and N-ethyl-2-pyrrolidylmethyl phenylcyclopentylglycolate. The assay method involves an acid hydrolysis of the esters, the extraction of the resulting alcohols, and the infrared spectrophotometric determination of the ratio of the resulting alcohols. For standardization, samples of pure *N*-ethyl-3-hydroxypiperidine and *N*-ethyl-2-hydroxymethylpyrrolidine were prepared. Fig. 1 shows the infrared spectra in the 8-11-μ region for these two compounds. The piperidyl compound exhibits an absorption minimum at 8.35 μ and a maximum[1] at 10.08 μ whereas for the pyrrolidyl compound, this minimum and maximum are exactly reversed. These two points were therefore chosen for the determination of the ratio of these two compounds in their mixtures. Using these two compounds, standard mixtures were prepared in carbon disulfide solution such that the total concentration was about 175 mg. in 3 cc. Fig. 2 shows the spectra for these mixtures where the pyrrolidyl compound was 48.86, 63.46, and 78.81%. The absorbance (I_0–I) of each solution was determined by reading the transmission for carbon disulfide (I_0) and for the carbon disulfide solution of the mixed alcohols (I) at 8.35 μ ($\pm$0.03 μ) using a sodium chloride cell with a 0.10-mm. light path and a salt plate in the reference beam. The absorbance ratio R was then calculated by the formula

$$R = \frac{(I_0 - I)10.08\ \mu}{(I_0 - I)8.35\ \mu}$$

and R was plotted on centimeter paper against the per cent of pyrrolidyl alcohol in the corresponding solution. Fig. 3 shows the function to be a straight line for mixtures of 50%

(10) L. G. Abood and F. Rinaldi, *Psychopharmacologia*, **1**, 117 (1959).

(11) L. G. Abood and L. J. Meduna, *J. Nervous Mental Diseases*, **127**, 546 (1958).

(12) L. J. Meduna and L. G. Abood, *J. Neuropsych.* **1**, 1 (1960).

(13) S. Gershon, *Nature*, **186**, 1072 (1960).

(14) L. G. Abood, A. Ostfeld and J. H. Biel, *Arch. Int. pharmacodyn.*, **120**, 186 (1959).

(15) All infrared spectra were determined on a Beckman IR-5 double beam spectrophotometer.

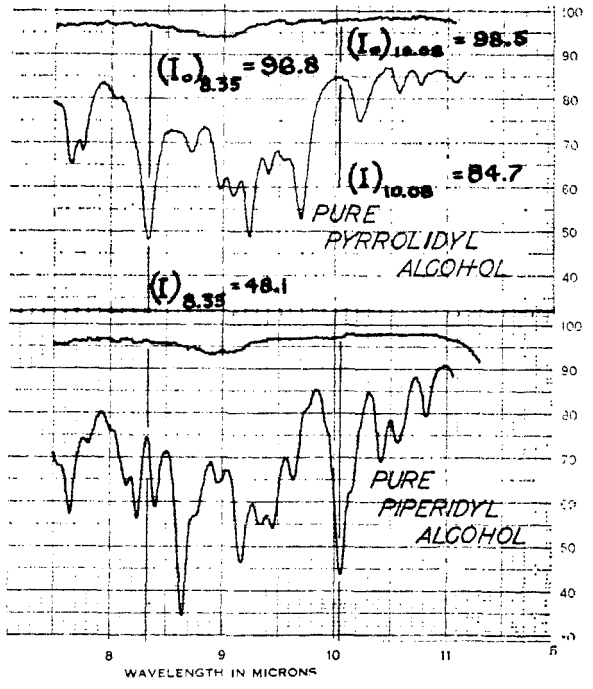


Figure 1

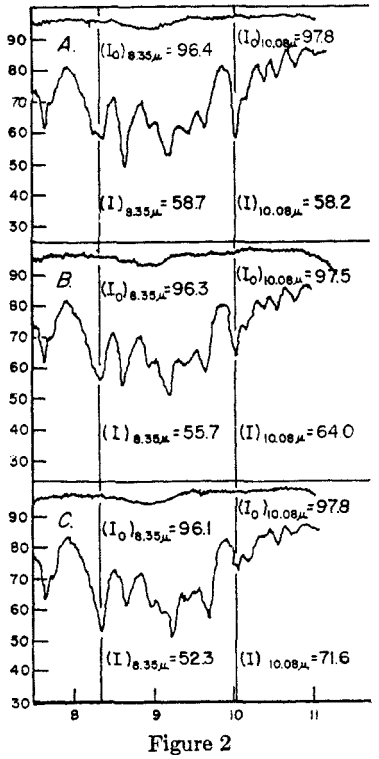


Figure 2

to 100% of pyrrolidyl alcohol and 50% to 0% of piperidyl alcohol. The equation for this curve was found to be

$$P = \frac{1.7592 - R}{0.01469}$$

where P = per cent of pyrrolidyl alcohol and R = the absorbance ratio,

$$\frac{(I_0 - I)_{10.08\ \mu}}{(I_0 - I)_{8.35}}$$

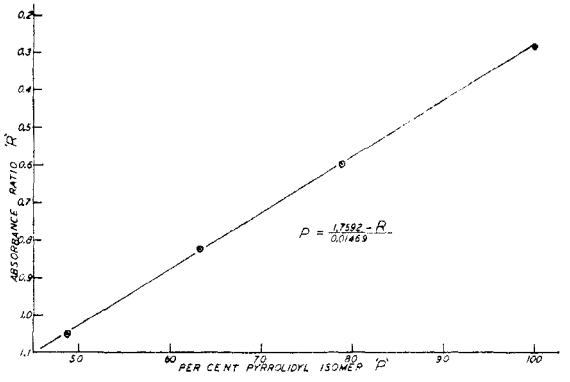


Figure 3

In order to prove that ring contraction actually did take place during esterification of the *N*-ethyl-3-chloropiperidine, samples of the two esters were prepared by ester interchange using the pure *N*-ethyl-3-hydroxypiperidine and the *N*-ethyl-2-hydroxymethylpyrrolidine. Subsequent acid hydrolysis of each of these esters yielded alcohol fragments with infrared spectra identical to that of the starting alcohols. This experiment showed that no change takes place in the ring structure of the cyclic amino alcohols during esterification by ester interchange and it established the validity of the assay method in that it showed that no change takes place in the structure of the alcohol fragments during the hydrolysis procedure. Fig. 4 shows the spectra of the mixture of alcohols resulting from the hydrolysis of a typical batch of the ester prepared through the halopiperidine. When Fig. 4 is compared to curve B of Fig. 2, which shows a standard mixture of alcohols of similar ratio, it can be seen that qualitatively these charts are identical in every respect. This, of course, shows that ring contraction does occur during the esterification of the halopiperidine resulting in a mixture of isomers.

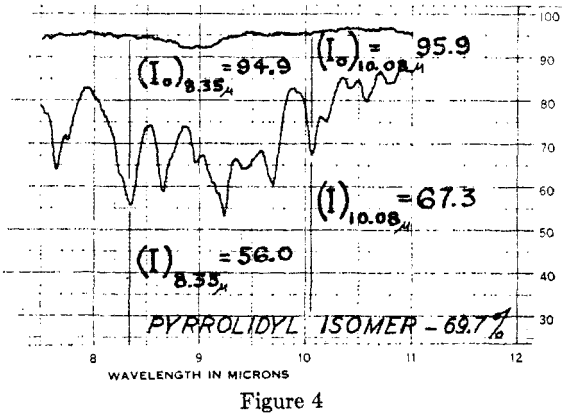


Figure 4

Method for Assay. Reagents. 1. Sulfuric acid, A.R. 2. Sodium hydroxide pellets, C.P. 3. Carbon disulfide, A.R. 4. Diethyl ether, anhydrous, A.R., stored over sodium wire before use.

Procedure. A 0.5-g. sample was dissolved in 20 cc. of water in a flask, chilled in an ice bath, 10 cc. of concd. sulfuric acid was added and the mixture refluxed for 1 hr. The solution was cooled and transferred through a pledget of glass wool to a separatory funnel equipped with a Teflon plug stopcock using a minimum of water for the transfer. The cooled solution was then extracted with two 50-cc. portions of ether. The aqueous phase was returned to a boiling flask and held in an ice bath while 16 g. of solid sodium hydroxide was added with rapid stirring to avoid excessive heating. If the salts crystallized excessively, a small amount of water was added; however, after the addition of alkali was complete, a

small amount of undissolved salt or sodium hydroxide was essential to insure saturation. The solution was decanted as thoroughly as possible from the precipitated salts into a separatory funnel equipped with a Teflon plug stopcock. The flask and residue were washed with several portions of anhydrous ether prepared by storage over sodium wire and the washings added to the separatory funnel. The aqueous phase was extracted with two 50-cc. portions of anhydrous ether. The extracts were passed through a No. 42 Whatman paper and pooled in a small suction flask. It was not necessary that the above transfers be strictly quantitative since the assay depends upon a measurement of the ratio of the resulting alcohols rather than total concentration. The ether was evaporated to a volume of 3 to 5 cc. in a manner such that contamination with moisture was avoided. The evaporation of the ether was then completed under vacuum without heat. The residue was dissolved in 3 cc. of carbon disulfide and transmission readings were made on this solution in a 0.1-mm. sodium chloride cell as described in the standardization procedure.

Calculations: Per cent. of pyrrolidyl isomer = 1.7592-R/0.01469 where R = the ratio of transmissions as described in the standardization procedure. Per cent of piperidyl isomer = 100 − per cent of pyrrolidyl isomer.

Reaction of N-ethyl-3-chloropiperidine with benzilic acid. A. N-Ethyl-3-piperidyl benzilate hydrochloride. A mixture containing 22 g. (0.15 mole) of *N*-ethyl-3-chloropiperidine and 34.2 g. (0.15 mole) of benzilic acid was dissolved in 400 cc. of dry isopropyl alcohol and the solution refluxed for 12 hr. The solvent was removed by distillation, the residue taken up in water, made alkaline with potassium carbonate solution and the organic phase extracted with ether. The combined ether extracts were dried with potassium carbonate, the ether removed by distillation and the basic ester residue converted to the hydrochloride salt in isopropyl alcohol; 50 g. (89%) of a solid was obtained, m.p. 153–155°. Recrystallization of the solid from 500 cc. of isopropyl alcohol yielded 33 g. of solid material, m.p. 163–167° which contained 55% of the 3-piperidyl ester (by infrared assay). The mother liquor from the recrystallization was set aside (mother liquor A) for part B of the experiment. The solid melting at 163–167° was recrystallized twice from ethanol yielding 12.5 g. of the pure (infrared assay) 3-piperidyl ester, m.p. 191–192°. A mixed melting point with an authentic sample of the ester (prepared by the unequivocal ester interchange method) showed no depression.

B. *N-Ethyl-2-pyrrolidylmethyl benzilate hydrochloride.* Mother liquor A from part A was concentrated to one-fourth its original volume and 12.5 g. of a solid isolated, m.p. 145–147°, which was the pure (infrared assay) pyrrolidylmethyl ester.

Reaction of N-ethyl-3-chloropiperidine and phenylcyclopentylglycolic acid (I). A mixture consisting of 108.9 g. (0.50 mole) of phenylcyclopentylglycolic acid, 81.1 g. (0.55 mole) of *N*-ethyl-3-chloropiperidine and 625 cc. of isopropyl alcohol was refluxed for 40 hr. The solution was concentrated to dryness *in vacuo*, the residue dissolved in 1000 cc. of water (*p*H 4) and extracted with ether to remove any unchanged acid. The solution was then saturated with sodium bicarbonate and the product isolated by extraction of the alkaline mixture with ether. The combined ether extracts were dried over magnesium sulfate and the ether was removed by distillation.

Hydrochloride salt. A solution in 500 cc. of acetone was acidified with ethereal hydrochloric acid to *p*H 2. The solid was removed by filtration, washed with acetone and dried at 90°; yield 111.5 g. (60.7%), m.p. 179–181°. A 91.5-g. sample was recrystallized from 550 cc. of acetonitrile and a constant melting mixture isolated, yield 52 g. (57%), m.p. 188–189°.

Anal. Calcd. for $C_{20}H_{30}ClNO_3$: N, 3.81; Cl, 9.66. Found: N, 3.80; Cl, 9.65.

The average isomer ratio from various experiments of 2-pyrrolidylmethyl *vs.* 3-piperidyl ester was found to be 70:30 ± 5%, respectively, as determined by the infrared spectroscopy method outlined above. The filtrate was concentrated to dryness and the residue (35.3 g.) was recrystallized from 50 cc. of acetonitrile, yield 30.8 g. (34%), m.p. 177–178°.

Anal. Calcd. for $C_{20}H_{30}ClNO_3$: N, 3.81; Cl, 9.66. Found: N, 3.76; Cl, 9.50.

The isomer ratio was the same as for the higher melting material. The lower melting point may be due to a different diastereoisomeric mixture.

N-Ethyl-3-piperidyl phenylcyclopentyl glycolate hydrochloride (II). *Procedure A.* A mixture consisting of 106.0 g. (0.45 mole) of methyl phenylcyclopentylglycolate, 64.5 g. (0.50 mole) of *N*-ethyl-3-hydroxypiperidine, 1.5 g. of sodium methoxide and 1,250 cc. of heptane was refluxed until 26 cc. of methanol had distilled. The catalyst was removed by filtration, and the filtrate washed three times with 200 cc. of water. The organic phase was dried over potassium carbonate and the solvent distilled. The residue of free basic ester weighed 136.5 g. (91%). It was dissolved in 1000 cc. of acetone and acidified with ethereal hydrochloric acid to *p*H 2. The solid was isolated by filtration and dried at 90°; yield 112 g. (74%), m.p. 200–201°. The solid was recrystallized from 2000 cc. of isopropyl alcohol, yield 88 g., m.p. 214–216°.

Anal. Calcd. for $C_{20}H_{30}ClNO_3$: N, 3.81; Cl, 9.66. Found: N, 3.83; Cl, 9.63.

According to the infrared spectroscopy method, this material was the pure 3-piperidyl ester.

Procedure B. Fifty-five grams of the 70:30 mixture of 2-pyrrolidylmethyl and 3-piperidyl ester, respectively, of experiment I melting at 188–189° was converted to the free base esters with aqueous sodium bicarbonate, extracted with ether and the high-boiling ester distilled *in vacuo*, b.p. 166–168° (0.05 mm.), yield 45 g. (91%).

Anal. Calcd. for $C_{20}H_{29}NO_3$: N, 4.23. Found: N, 4.26.

Conversion of the base to the hydrochloride salt in acetone with ethereal hydrochloric acid produced a solid melting at 207–208°, yield 36.5 g. (77%). Recrystallization from acetonitrile yielded 21 g. (52%) of the high melting diastereoisomer, m.p. 232–233° which was the pure (infrared assay) 3-piperidyl ester. The filtrate was concentrated to dryness and the residue recrystallized from acetonitrile, m.p. 212–213°, yield 9.0 g. (22%). In subsequent runs this yield was as high as 40%. A mixed melting point with the product of procedure A caused no depression. The infrared assay showed this compound to be pure 3-piperidyl ester.

N-Ethyl-2-pyrrolidylmethanol (III). A mixture consisting of 5.6 g. (0.1 mole) of potassium hydroxide, 10.1 g. (0.1 mole) of 2-pyrrolidylmethanol,[16] 11 g. (0.1 mole) of ethyl bromide and 100 cc. of ethanol was placed in a pressure bottle, which was heated at 100° for 2 hr. The sodium bromide was removed by filtration, and the product collected by distillation; b.p. 50–51° (2.8 mm.), yield 9.0 g. (68.8%), n_D^{25} 1.4678.

Anal. Calcd. for $C_7H_{15}NO$: N, 10.83. Found: N, 10.98.

N-Ethyl-2-pyrrolidylmethyl phenylcyclopentylglycolate hydrochloride (IV). A mixture consisting of 10.6 g. (0.08 mole) of *N*-ethyl-2-pyrrolidylmethanol, 19.3 g. (0.08 mole) of methyl phenylcyclopentylglycolate, 1.0 g. of sodium methoxide and 200 cc. of heptane was refluxed for 4 hr., while 5 cc. of methanol was collected by distillation. The catalyst was removed by filtration, and the filtrate was washed three times with 100 cc. of water. The organic phase was dried over magnesium sulfate and the solvent distilled. The residue of the basic ester weighed 23.7 g. (89.5%). It was dissolved in 300 cc of ether and the ether solution acidified with ethereal hydrochloric acid to *p*H 2. The solid was isolated by filtration, dried at 90°, yield 21.3 g. (84%), m.p. 170–172°. Recrystallization from 175 cc. of acetonitrile yielded 14 g., m.p. 185–186°; $\lambda_{max}^{Nujol}\mu$ 3.03 (OH); 5.75 (ester C=O); 8.15 (ester C—O—C); 13.83 and 14.2, 14.3 (monosubstituted benzene).

(16) F. F. Blicke and Chi-Jung Lu, *J. Am. Chem. Soc.*, **77**, 29(1955).

Anal. Calcd. for $C_{20}H_{30}ClNO_3$: C, 65.29; H, 8.22; N, 3.81; Cl, 9.66. Found: C, 65.42; H, 8.15; N, 3.83; Cl, 9.77.

This material was shown to be pure 2-pyrrolidylmethyl ester by the infrared assay method.

N-(β-Benzyloxyethyl)-3-hydroxypiperidine (V). To a refluxing mixture of 65.6 g. (0.66 mole) of 3-hydroxypiperidine and 150 cc. of dry toluene was added 56.5 g. (0.33 mole) of β-benzyloxyethyl chloride and the mixture allowed to reflux for 6 hr. The 3-hydroxypiperidine hydrochloride was removed by filtration, the filtrate concentrated *in vacuo*, and the product collected by distillation; b.p. 150° (1.1 mm.), yield 60.0 g. (77.3%), n_D^{25} 1.5321.

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.46; H, 9.00; N, 5.95. Found: C, 71.37; H, 9.03; N, 5.95.

N-(β-Benzyloxyethyl)-3-piperidyl benzilate hydrochloride (VI). A mixture consisting of 38.8 g. (0.16 mole) of V, 36.3 g. (0.15 mole) of methyl benzilate, 0.6 g. of sodium methoxide and 400 cc. of heptane was refluxed until 9.3 cc. of methanol had distilled. The catalyst was removed by filtration, the filtrate washed twice with 100 cc. of water, dried over potassium carbonate, and the solvent removed by distillation; yield 67.0 g. (100%). The ester base was dissolved in 300 cc. of acetone, acidified to *p*H 3 with ethereal hydrochloric acid, and the solid hydrochloride separated by filtration, yield 67.3 g. (93%), m.p. 167–168°. The crude salt was recrystallized from 250 cc. of methanol, yield 50.0 g. (69%), m.p. 172°; λ_{max}^{Nujol} (μ) 3.11 (OH); 5.75 (ester C=O); 8.21 (ester C—O—C); 9.00 (ether C—O—C); 13.21, 13.35, 13.62 and 14.12, 14.31 (monosubstituted benzene).

Anal. Calcd. for $C_{28}H_{32}ClNO_4$: C, 69.77; H, 6.69; N, 2.90; Cl, 7.36. Found: C, 69.83; H, 6.79; N, 2.91; Cl, 7.30.

N-(β-Hydroxyethyl)-3-piperidyl benzilate hydrochloride (VII). A mixture consisting of 24.1 g. (0.05 mole) of VI, 3.0 g. of 10% palladium-on-charcoal, and 150 cc. of methanol was reduced in a Parr hydrogenator at 25° and 60 p.s.i. of hydrogen. The catalyst was removed by filtration, the filtrate concentrated to dryness *in vacuo*, and the residue triturated with anhydrous ether, yield 18.2 g. (98.5%), m.p. 150–151°; λ_{max}^{Nujol} (μ) 3.03 (OH); 5.77 (ester C=O); 8.17 (ester C—O—C); 13.28, 13.68 and 14.19, 14.30 (monosubstituted benzene).

Anal. Calcd. for $C_{21}H_{26}ClNO_4$: C, 64.36; H, 6.69; N, 3.57; Cl, 9.06. Found: C, 64.35; H, 6.71; N, 3.57; Cl, 8.99.

3-Piperidyl benzilate hydrochloride (VIII). A mixture consisting of 20.0 g. (0.05 mole) of *N*-benzyl-3-piperidyl benzilate, 3.0 g. (0.05 mole) of glacial acetic acid, 3.5 g. of 10% palladium-on-charcoal, and 200 cc. of methanol was reduced in a Parr hydrogenator at 25° and 60 p.s.i. The catalyst was removed by filtration, the filtrate acidified to *p*H 3 with ethereal hydrochloric acid, and concentrated to dryness *in vacuo*. The residue was triturated with anhydrous ether; yield 16.8 g. (96.5%), m.p. 178–180°; λ_{max}^{Nujol}(μ) 3.00 (OH); 5.73 (ester C=O); 8.19 (ester C—O—C); 13.05, 13.30, 13.68 and 14.28 (monosubstituted benzene).

1-[β(3-Hydroxypiperidino)ethyl]-4-methylpiperazine (IX). To a mixture of 14.3 g. (0.36 mole) of sodium hydroxide, 36.0 g. (0.36 mole) of 3-hydroxypiperidine and 300 cc. of 90% ethanol was added at reflux temperature 42 g. (0.18 mole) of β-(4-methylpiperazino)ethyl chloride dihydrochloride dissolved in 250 cc. of 80% ethanol. After refluxing the mixture for 3 hr., the inorganic salt was filtered, and the filtrate concentrated to dryness *in vacuo*. The residue was dissolved in 150 cc. of water, the aqueous solution saturated with sodium hydroxide, and the oily layer separated by extraction of the alkaline mixture with tetrahydrofuran. The combined extracts were dried over potassium carbonate and the product collected by distillation, b.p. 120–122° (0.6 mm.), yield 16.3 g. (40.3%), n_D^{25} 1.5061.

Anal. Calcd. for $C_{12}H_{25}N_3O$: N, 18.48. Found: N, 18.07.

N-(β-Dimethylaminoethyl)-3-hydroxypiperidine (X). To a solution containing 101.4 g. (1.0 mole) of 3-hydroxypiperidine in 500 cc. of dry benzene was added 53.8 g. (0.5 mole) of β-dimethylaminoethyl chloride (freshly distilled) and the mixture was refluxed for 4 hr. The 3-hydroxypiperidine hydrochloride was removed by filtration, the filtrate concentrated *in vacuo*, and the product was collected by distillation; b.p. 92–94° (0.9 mm.), yield 73.2 g. (85%), n_D^{25} 1.4822.

Anal. Calcd. for $C_9H_{20}N_2O$: N, 16.26. Found: N, 16.15.

α-(3-Hydroxypiperidino) acetal (XI). A mixture consisting of 68 g. (0.67 mole) of 3-hydroxypiperidine, 67 g. (0.67 mole) of triethylamine, 132 g. (0.67 mole) of α-bromo acetal and 400 cc. of dry toluene was refluxed for 4 hr. The triethylamine hydrobromide was filtered off. The filtrate was washed with saturated aqueous potassium carbonate solution and then dried over anhydrous potassium carbonate; the product was collected by distillation; b.p. 98–100° (0.6 mm.), yield 91 g. (62.5%), n_D^{25} 1.4632.

Anal. Calcd. for $C_{11}H_{23}NO_3$: N, 6.44. Found: N, 6.65.

1-Methyl-4-[β-(3-hydroxypiperidino)ethylamino]piperazine (XII). To 75 cc. of concd. hydrochloric acid at 0–5° under a nitrogen atmosphere was added 32.6 g. (0.15 mole) of XI. After standing at 25° for 3 hr., the solution was concentrated to dryness with a 50° water bath under vacuum. The residue was diluted to 150 cc. with water, neutralized to *p*H 7 with 14 g. (20%) of aqueous sodium hydroxide, and 17.5 g. (0.15 mole) of 1-amino-4-methylpiperazine[17] was added at 0–5°. The solution stood overnight at 25° and was saturated with sodium hydroxide. The oil was extracted from the aqueous solution with three 100-cc. portions of tetrahydrofuran, the combined extracts were dried over potassium carbonate, and concentrated to dryness *in vacuo*, yield 32.4 g. (90%) of crude hydrazone.

To 5.2 g. (0.14 mole) of lithium aluminum hydride in 200 cc. of tetrahydrofuran at reflux was added a solution of crude hydrazone in 100 cc. of tetrahydrofuran. The mixture was refluxed for 4 hr. and the complex decomposed with 20 cc. (40%) of aqueous potassium hydroxide. The inorganic salts were removed by filtration, the filtrate dried over potassium carbonate, and the product collected by distillation; b.p. 147–149° (0.03 mm.), yield 23.7 g. (72.5%).

Anal. Calcd. for $C_{12}H_{26}N_4O$: C, 59.47; H, 10.82; N, 23.11. Found: C, 59.50; H, 10.95; N, 22.85.

1-Amino-3-hydroxypiperidine (XIII). To a solution of 50.5 g. (0.50 mole) of 3-hydroxypiperidine and 50.5 g. of water was added 128.0 g. (0.39 mole) of 30% sulfuric acid with stirring and cooling. To the above solution at 10–15° was added a solution of 85.0 g. (1.23 mole) of sodium nitrite and 150 cc. of water during a period of 1 hr. The solution was stirred at 25° for another hour and the oily layer extracted from the aqueous phase with chloroform. The combined extracts were washed with 40% aqueous potassium hydroxide, dried over potassium carbonate and concentrated to dryness, leaving a residue of 40.9 g. (62.8%).

To 17.5 g. (0.45 mole) of lithium aluminum hydride in 500 cc. of tetrahydrofuran was added a solution of 40.9 g. (0.32 mole) of *N*-nitroso-3-hydroxypiperidine in 300 cc. of tetrahydrofuran within a period of 90 min. The mixture was refluxed for 1 hr. and the complex decomposed with 100 cc. of 40% aqueous potassium hydroxide. The inorganic salts were filtered, the filtrate dried over potassium carbonate, and the product collected by distillation, b.p. 84–86° (0.45 mm.), yield 25.9 g. (71.0%).

Anal. Calcd. for $C_5H_{12}N_2O$: C, 51.70; H, 10.42; N, 12.05. Found: C, 51.42; H, 10.59; N, 12.04.

N-Formylamino-3-hydroxypiperidine (XIV). A mixture of 60.0 g. (0.52 mole) of *N*-amino-3-hydroxypiperidine and 38.5 g. (0.52 mole) of ethyl formate was refluxed for 5 hr. The product was collected by distillation; b.p. 165° (1.2 mm.), yield 41.5 g. (55.4%).

Anal. Calcd. for $C_6H_{12}N_2O_2$: N, 19.44. Found: N, 19.72.

N-Methylamino-3-hydroxypiperidine (XV). To 13.3g. (0.35 mole) of lithium aluminum hydride in 500 cc. of tetrahydrofuran was added a solution of 40.3 g. (0.28 mole) of XIV and 250 cc. of tetrahydrofuran within 90 min. The mixture was refluxed for 3 hr. and the complex decomposed with 40 cc. of 40% aqueous potassium hydroxide. The inor-

(17) E. A. Conroy, U.S. Patent **2,663,706**, Dec. 22, 1953.

ganic salts were removed by filtration, the filtrate dried over potassium carbonate, and the product collected by distillation; b.p. 83–86° (1.2 mm.), yield 25.9 g. (71.2%), n_D^{25} 1.4972.

Anal. Calcd. for $C_6H_{14}N_2O$: N, 10.78. Found: N, 11.03.

N-Benzyl-4-hydroxypiperidine (XVI). A mixture consisting of 50.0 g. (0.5 mole) of 4-hydroxypiperidine, 50.0 g. (0.5 mole) of triethylamine, 62.5 g. (0.5 mole) of benzyl chloride and 250 cc. of dry toluene was refluxed for 4 hr. The triethylamine hydrochloride was filtered off, the filtrate concentrated, and the product collected by distillation, b.p. 122–123° (0.7 mm.); yield 65.0 g. (69%), n_D^{25} 1.5514.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.34; H, 8.96; N, 7.32 Found: C, 74.62; H, 8.77; N, 6.98.

Acknowledgment. We are indebted to Dr. H. L. Friedman for his many valuable suggestions and Dr. H. L. Daiell for his continued interest and support of this study.

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Notes A department for short papers of immediate interest.

Sulfonamides and Some Related Materials[1]

H. LEIGHTON MORRILL, GEORGE W. STEAHLY, AND FERDINAND B. ZIENTY

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In connection with the investigation of the effect of acyl substituents on the therapeutic activity of sulfonamide-related materials, acyl derivatives of sulfanilamide, sulfathiazole, 2-amino-5-thiazolyl-*p*-nitrophenyl sulfide,[2] and 2-amino-5-thiazolyl-*p*-nitrophenyl sulfone[2] were required (Tables I and II). Synthesis was accomplished conveniently by reaction of the amino compound with the appropriate anhydride (diglycolic,[3] thiodiacetic,[3] benzylsuccinic, and tetrachlorophthalic) and in most cases the desired product crystallized out of the reaction medium. In the reactions with thiodiacetic anhydride it was essential to use a substantial molar excess of the anhydride in order to avoid formation of oily or colored products which led to difficulties on purification.

The benzylsuccinyl derivatives (Compounds II and V) made from benzylsuccinic anhydride[4] are considered to be the β-amides in accordance with the Anschutz Rule.[5] This assignment of structure is supported further by the fact that high yields of pure products are obtained.

The aminophenyl compounds (VIII and X) were made by ammoniacal iron acid reduction of the corresponding nitrophenyl derivatives.

Convenient laboratory methods were devised for making diglycolic and thiodiacetic anhydrides.

EXPERIMENTAL[6]

Diglycolic anhydride.[7] In a 500-ml. flask fitted with a column equivalent to eight theoretical plates there were placed 49 g. of diglycolic acid (0.37 mole), 139 ml. of acetic anhydride (1.48 moles) and 3 drops of phosphoric acid. The solution was heated sufficiently to maintain a slow rate of distillation of acetic acid. When the vapor temperature at the top of the column reached about 127°, heating was increased and about 25 ml. of acetic anhydride was distilled forward. The flask was fitted with a 1 × 13 cm. still head packed with 1–16″ glass helices. The remaining acetic anhydride was distilled at 100 mm. absolute pressure. Then the diglycolic anhydride was distilled at 140° (35 mm.). Yield, 33.2 g. (78%). A sample recrystallized from benzene melted at 91–93°.

Thiodiacetic anhydride.[8] A mixture of 64.8 g. (0.4 mole) of thiodiacetic acid (assaying 92.5%), 18.4 g. (0.134 mole) of phosphorus trichloride, and 80 ml. of chloroform was warmed at 55–57° with stirring until no more hydrogen chloride was evolved. Then the mixture was refluxed for 1 hr., 9.2 g. (0.067 mole) of phosphorus trichloride was added, and refluxing was continued for one more hour. The hot chloroform solution was decanted through a filter, the residue on the filter was washed with a small amount of chloro-

(1) Part of a presentation at the Frederick F. Blicke Symposium of the Division of Medicinal Chemistry at the 138th National Meeting of the American Chemical Society, New York, N. Y., September, 1960.

(2) L. L. Bambas, *J. Am. Chem. Soc.*, **67**, 671 (1945).

(3) Some related diacyl *N,N'*-diaminodiphenyl sulfones were described by L. P. Kyrides, U. S. Patents **2,399,600** (April 30, 1946) [*Chem. Abstr.*, **40**, 4180 (1946)] and **2,413,833-2,413,835** (January 7, 1947) [*Chem. Abstr.*, **41**, 2749–50 (1947)].

(4) J. Binapfl, U. S. Patent **2,121,183** (June 21, 1938) [*Chem. Abstr.*, **32**, 6259⁷ (1938)]; German Patent **607,380** (January 2, 1935) [*Chem. Abstr.*, **29**, 1834⁹ (1935)].

(5) R. Anschutz, C. Hahn, and P. Walter, *Ann.*, **354**, 136 (1907), showed the β-amide was obtained in the reaction of phenylsuccinic anhydride with aniline.

(6) All melting points are corrected.

(7) Preparation from diglycolic acid with acetyl chloride was described by R. Anschutz, *Ann.*, **259**, 190 (1890) and with phosphorus pentasulfide by R. Anschutz and F. Biernaux, *Ann.*, **273**, 64 (1893).

(8) Preparation by reaction of thiodiacetic acid with acetyl chloride was described by R. Anschutz and F. Biernaux, *Ann.*, **273**, 68 (1893), and by direct distillation of thiodiacetic acid by L. C. Lappas and G. L. Jenkins, *J. Am. Pharm. Assoc.*, **41**, 257 (1952). In our work, the acetic anhydride method shown above for diglycolic anhydride gave poor results with thiodiacetic acid; the thiodiacetic anhydride could not be distilled out of the reaction mixture without decomposition and crystallization proved difficult.