passed through a column of chromatographic grade activated alumina just before use to completely remove any traces of peroxide.

N-Bromosuccinimide was recrystallized from water and dried over concentrated sulfuric acid in a vacuum desiccator (m.p. 174.5–178.5°).

N-Bromophthalimide was recrystallized from glacial acetic acid and melted at 204–206° after drying as for N-bromosuccinimide.

2,3-Dibromotetrahydropyran (IV) and 3-bromo-5,6-dihydro-4*H*-pyran (III) were prepared as previously described.[5]

Reaction Procedure.—A 120-ml. portion of a 0.25 *M* dihydropyran solution in carbon tetrachloride (0.03 mole) was combined with 0.024 moles of N-bromophthalimide (or N-bromosuccinimide) and heated in a water bath under a reflux condenser equipped with a drying tube. The reaction time was measured as the interval between the falling of the first drop from the condenser and the disappearance of the last particles of N-bromophthalimide (or N-bromosuccinimide). On cooling to room temperature, phthalimide (m.p. 234–238°) or succinimide (m.p. 123–124°) separated from the solution. The imides were identified by their infrared spectra and by mixture melting points with known samples.

Isolation of Reaction Products.—Additional phthalimide was obtained after removal of part of the solvent to give a total yield of 18% based on N-bromophthalimide. Most of the solvent and unchanged dihydropyran (I) were removed under reduced pressure. The distillate was collected in a receiver cooled with ice and followed by a Dry Ice–acetone trap. Titration of the distillate with bromine gave the values for unchanged I reported in Table I after correcting for the excess initially present.

The adduct II was obtained from the concentrated solution in a 64% yield after washing with carbon tetrachloride. It melted at 144–146° when recrystallized from either acetone–water or ethanol (lit.[6] m.p. 144°). This compound gave no evidence of reaction with silver acetate in acetic acid solution even after one month at room temperature. It also failed to show any evidence of reaction on refluxing overnight in absolute ethanol.

The liquid remaining after removal of II was stripped of residual solvent and distilled slowly at about 5 mm. until the residue began to resinify. The distillate was shown to be III (4.7% yield based on N-bromophthalimide) by comparison of the infrared spectrum with one from a known sample.

Analytical Procedure.—Reaction mixtures of N-bromophthalimide (or N-bromosuccinimide) and dihydropyran were prepared as described, and after cooling and filtration, identical 50-ml. aliquots were taken for analysis. The quantitative procedure for detecting allylic or other reactive halides in the reaction mixture has already been described.[5]

Reaction in Ethanol.—2-Ethoxy-3-bromotetrahydropyran was obtained by reaction of N-bromophthalimide with I in absolute ethanol by the procedure previously used for the corresponding reaction with N-bromosuccinimide.[5] A 44% yield of product was obtained (based on N-bromophthalimide) which was identified by infrared and by preparation of a 2,4-dinitrophenylosazone derivative identical to one prepared from the product of the same reaction with N-bromosuccinimide, and also from II, as described in the next section.

Preparation of Osazone Derivatives.—The addition product II was converted to the 2,4-dinitrophenylosazone of 2,5-dihydroxypentanal by the procedure used to obtain the identical derivative from the adduct of I with N-bromosuccinimide.[5] The osazone, as prepared from II, started to precipitate within 1 hr. After recrystallization from ethanol–ethyl acetate and then ethanol, the bright orange crystals melted at 240–241° with decomposition (lit.[11] m.p. 242°).

Reaction of 2,3-Dibromotetrahydropyran (IV) with N-Bromophthalimide.—A solution of 2,3-dibromotetrahydropyran (IV) made by titration of 10 ml. of 0.25 *M* I in carbon tetrachloride with 0.263 *M* bromine in carbon tetrachloride was added over a period of 20 min. to N-bromophthalimide (0.565 g., 0.0025 mole) in 50 ml. of carbon tetrachloride while refluxing. The solution was cooled to room temperature and filtered to remove the crystals of phthalimide (0.36 g., 97.6% yield based on N-bromophthalimide). Bromine was observed to be present in the filtrate, and comparison with the color of known amounts of bromine in carbon tetrachloride showed the presence of 28% based on N-bromophthalimide.

(11) C. D. Hurd and C. D. Kelso, *J. Am. Chem. Soc.*, **70**, 1484 (1948).

1,1-Azaspiro Compounds[1]

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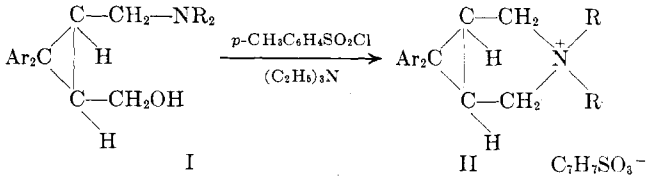
Syntheses of five-, six-, and seven-membered bicyclic 1,1-azaspiro systems have been rendered possible through the cyclization of suitable tertiary aminocarbinols using *p*-toluenesulfonyl chloride in the presence of tertiary bases (preferably triethylamine) as solvents.

The classical method for the synthesis of bicyclic azaspiro systems has been the reaction between a cyclic amine and α,ω-dihaloalkanes.[2] Several modifications of the same general procedure also have been employed. However, these require somewhat drastic conditions of fusion. The yields in most cases have not been reproducible and the 1,1-azaspiro compounds have not been the major product[3,4] of the reaction.

We wish to report a synthetic method for the formation of 1,1-azaspiro bi- and tricyclic compounds in excellent yields under mild conditions of reaction. The isolation and purification of the product of the reaction entails no ambiguity. By this procedure we have synthesized five-, six-, and seven-membered bi- and tricyclic 1,1-azaspiro systems.

In the course of the investigation of the aminoalcohols[5] of type I, when they were treated with *p*-toluenesulfonyl chloride in the presence of tertiary bases (pyridine or triethylamine) no sulfonic ester was isolated; either the starting aminoalcohol was recovered or the entire product had the properties of a quaternary salt.



When a cyclic amine was employed 1,1-azaspiro compounds were obtained.

(1) A portion of this material was presented before the Division of Organic Chemistry, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962, Abstracts, p. 25Q.

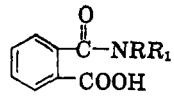
(2) H. R. Ing, "Heterocyclic Compounds," Vol. III, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p. 426.

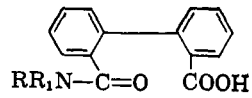
(3) D. M. Hall and F. Minhaj, *J. Chem. Soc.*, 4584 (1957).

(4) S. R. Ahmed and D. M. Hall, *ibid.*, 3043 (1958).

(5) R. Baltzly, N. B. Mehta, P. B. Russell, R. E. Brooks, E. M. Grivsky, and A. M. Steinberg, *J. Org. Chem.*, **27**, 213 (1962).

TABLE I
AMIDO ACIDS

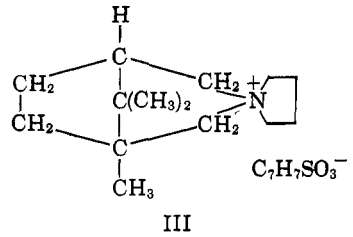

A


B

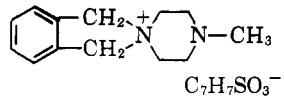
Compound no.	NRR_1	% Yield	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1A	$N(CH_2)_4$[a,b]							
2A	$N(CH_2)_4O$[b,c]							
3A	$N(CH_2)_5$[d]	98	174–176	$C_{13}H_{15}NO_3$	66.9	66.8	6.4	6.3
4A	$N(CH_2)_4NCH_3$[e]	72	279–280	$C_{13}H_{16}N_2O_3$	62.9	62.8	6.5	6.2
1B	$N(CH_2)_4$[a]	80	208–209	$C_{18}H_{17}NO_3$[f]	73.3	73.4	5.8	5.8
2B	$N(CH_2)_4O$[c]	85	249–250	$C_{18}H_{17}NO_4$	69.4	69.2	5.5	5.2
3B	$N(CH_2)_5$[d]	82	156	$C_{19}H_{19}NO_2$	73.7	73.5	6.2	6.0
4B	$N(CH_2)_4NCH_3$[e]	85	145	$C_{19}H_{20}N_2O_3$	70.4	70.1	6.2	6.1

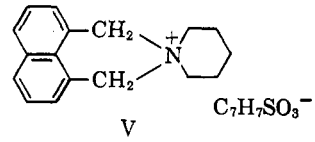
[a] Pyrrolidino. [b] Failed to crystallize from common organic solvents. [c] Morpholino. [d] Piperidino. [e] 1-Methylpiperazinyl. [f] Calcd. for N: 4.7. Found: 4.8.

This approach was extended to *cis*-1,3-substituted cyclopentanes[6] at once to ascertain if ease of cyclization was comparable and to prepare azaspiro camphidinium salts such as III, not readily accessible by simple alkylation.


III

The present paper deals with the preparation of (1) 1,1-azaspirodihydroisoindoles (IV) and (2) 1,1-azaspiroazepines (VII) and 1,1-azaspirobenzisoquinoline (V).


IV


V

The usual procedure for the preparation of the aminocarbinols was to treat the suitable anhydride with appropriate secondary amines. The amido acids (Table I) were obtained in excellent yields and were readily crystallized from hot benzene, except for compounds 1A and 1B in Table I.

Reduction of these amido acids with lithium aluminum hydride was facile and the aminocarbinols (Table II) could be crystallized in most cases from ether–pentane mixtures. The bases also were converted to hydrochloride salts (Table II).

When the tertiary amino carbinols were warmed with *p*-toluenesulfonyl chloride dissolved in triethylamine, within a few minutes voluminous precipitates were formed which, on continued warming, were rapidly and quantitatively transformed into heavy pasty masses leaving clear solutions. Usually within half an hour at about 60° the reactions were completed. When about 10% excess of reagent was employed the yields of the azaspiro products were quantitative and no side products were obtained. Often with excess reagent and higher temperature (reflux temperature of the tertiary bases used as solvents) the products obtained were dark. However, they could be decolorized easily with activated charcoal.

When less than one equivalent of the reagent was employed (as in the case of compounds 9A and 11A), the yield on the basis of the reagent was quantitative. For the preparation of large quantities of the products, it was desirable to heat the reaction mixtures at lower temperatures but for longer duration. When the reaction mixture was kept at room temperature for twelve hours, as in the case of 11B, the yield was lower; however, the unchanged aminocarbinol could be quantitatively recovered.

The isolation of the products of the reaction presented no unusual difficulties. After separating the solvent *in vacuo*, the quaternary salt, in most cases, was found to be fairly soluble in dry acetone and could be separated from triethylamine hydrochloride. The solvent was then evaporated and the residue subjected to high-vacuum sublimation[7] to remove traces of triethylamine hydrochloride. This process also was employed to remove gross amounts of that by-product when the rough separation just described failed because of low solubility of the quaternary salt in acetone. The product could then be easily crystallized from methanol–acetone mixture with the addition of ether to incipient turbidity (Table III). The tosylate anion could be subsequently displaced by iodide or bromide by treating the quaternary salt with sodium iodide or bromide in dry acetone.

The reaction of 1,8-naphthalic anhydride with piperidine to yield the desired amido acid was facilitated by the addition of trace amounts of *p*-toluenesulfonic acid. Reduction with lithium aluminum hydride gave 1-hydroxymethyl-8-piperidinomethylnaphthalene. Cyclization by the procedure outlined previously gave the desired azaspirobenzisoquinoline.

The ease of formation of the initial voluminous precipitate led us to suspect that it was the sulfonic ester, in which we were originally interested. Therefore, an attempt was made to isolate this presumptive intermediate and to cyclize it separately. In the course of the

(6) N. B. Mehta and R. E. Brooks, *J. Org. Chem.*, **27**, 1266 (1962).

(7) N. B. Mehta and J. Zupicich, *Chemist-Analyst*, **50**, 84 (1961).

TABLE II
AMINOALKANOLS

Compound no.	NRR1	% Yield	B.p. (μ),[e] M.p., °C.	Bases: Formula	Bases: Carbon, % Calcd.	Bases: Carbon, % Found	Bases: Hydrogen, % Calcd.	Bases: Hydrogen, % Found	Salts: M.p., °C.	Salts: Formula	Salts: Carbon, % Calcd.	Salts: Carbon, % Found	Salts: Hydrogen, % Calcd.	Salts: Hydrogen, % Found
5A	N(CH2)4[a]	80	105 (40)	C12H17NO	75.4	75.6	8.9	8.8	107–108	C12H17NO·HCl[f]	63.3	63.6	7.9	7.9
6A	N(CH2)4O[b]	82	55	C12H17NO2	69.6	69.9	8.2	8.1	165	C12H17NO2·HCl	59.1	58.8	7.4	7.7
7A	N(CH2)5[c]	85	70	C13H19NO[g]	76.1	76.0	9.3	9.6	155–156 efferv.	C13H19NO·HCl·0.5H2O	58.1	58.4	8.6	8.3
8A	N(CH2)4NCH3[d]	92	69–70	C13H20N2O	70.8	70.9	9.1	9.2	199–200	C13H20N2O·2HCl	52.4	52.3	7.6	7.4
5B	N(CH2)4[a]	84	114 (48)	C18H21NO[h]	80.9	80.9	7.8	7.8	156–157	C18H21NO·HCl[i]	71.2	71.2	7.3	7.1
6B	N(CH2)4O[b]	90	108–110	C18H21NO2[j]	76.3	76.6	7.4	7.5	304–305	C18H21NO2·HCl[k]	67.6	67.4	6.9	6.6
7B	N(CH2)5[c]	97	85–86	C19H23NO	81.1	80.8	8.2	8.3	101 effer.	C19H23NO·HCl·2H2O	64.5	64.6	7.9	7.6
8B	N(CH2)4NCH3[d]	96	95–96	C19H24N2O	77.0	76.8	8.1	7.9	268–270 dec.	C19H24N2O·2HCl[l]	61.8	61.7	7.0	6.8

[a] Pyrrolidino. [b] Morpholino. [c] Piperidino. [d] 1-Methylpiperazinyl. [e] Boiling point is actual furnace temperature. [f] Compound 5A (salt). Calcd. for N: 6.2. Found: 6.1. [g] Compound 7A (base). Calcd. for N: 6.8. Found: 6.7. [h] Compound 5B (base). Calcd. for N: 5.2. Found: 5.3. [i] Forms a stable hemihydrate, m.p. 125 (efferv.). [j] Compound 6B (base). Calcd. for N: 5.0. Found: 5.2. [k] Forms a stable hemihydrate, m.p. 118 (efferv.). [l] Compound 8B (salt). Calcd. for N: 7.6. Found: 7.7.

synthesis of dihydro-5-dibenz[*c,e*]azepinespirotetramethylene ammonium tosylate (VII) (compound 9B), a portion of the voluminous precipitate initially formed was removed and the reaction quenched by addition of ether. On working up the reaction mixture, *o*-pyrrolidinomethyl-*o'*-hydroxymethylbiphenyl-*p*-toluenesulfonate hydrochloride (VI), m.p. 170–171°, was obtained. Neither triethylamine hydrochloride nor the hydrochloride salt of the aminocarbinol (compound 5B) was found to be present. When this sulfonic ester hydrochloride was heated in triethylamine for an additional half hour, the azepine compound 9B (VII), identical to that obtained from the main batch of the original reaction, was isolated.

Despite the lack of coplanarity of the diphenyl system in the azepines, the cyclization was found to be very facile. Compounds of this type are asymmetric and, in principle, should be resolvable if the isomers have sufficient stability.

Experimental[8]

Data on amido acids, aminocarbinols, and their salts and 1,1-azaspiro compounds are reported in Tables I, II, and III, respectively. Those obtained from phthalic anhydride are indicated by lettering A, and those obtained from diphenic anhydride by lettering B. The preparations of a number of compounds not fitting these classifications are described separately. Typical procedures are also given in detail for the various operations. Melting points are corrected.

Phthalic Acid Mono-4-methylpiperazide (Compound 4A).—A mixture of 10 g. of phthalic anhydride and 70 ml. of freshly distilled 4-methylpiperazine was refluxed for 4 hr. On removal of the excess amine *in vacuo*, the thick oily product was triturated with ether. Crystallization from methanol–benzene mixtures gave prisms, m.p. 279–280°.

Diphenic Acid Monopiperidide (Compound 3B).—On mixing 10 g. (0.045 mole) of diphenic anhydride and 40 ml. of freshly distilled piperidine, an exothermic reaction was observed. The reaction mixture was refluxed for 2 hr. and the excess amine was removed *in vacuo*. The residue was dissolved in 5% sodium bicarbonate solution, filtered, and acidified with hydrochloric acid. The amido acid was recrystallized from benzene when 11.5 g. (82%), m.p. 155–156°, was obtained.

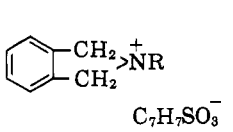
Others in the B series shown in Table I were prepared and purified by the same procedure, except the 4-methylpiperazine derivative. In that case, after the removal of excess amine, the glassy product was triturated with ether. It was then crystallized from benzene, m.p. 145°.

***o*-[4-Methylpiperazinylmethyl]benzyl Alcohol Dihydrochloride (Compound 8A).**—The solid amido acid, 12 g., compound 4A, was added portionwise through a powder addition funnel, to a rapidly stirred solution of 6.8 g. of lithium aluminum hydride in 800 ml. of anhydrous ether. After refluxing for 24 hr., 5 ml. of water and then 10 ml. of a 10% sodium hydroxide solution were added. The clear ethereal layer was separated, dried, and con-

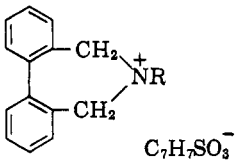
(8) Melting points are corrected.

TABLE III

AZASPIRO COMPOUNDS



A



B

Compound no.	N-R	% Yield	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
9A	$N(CH_2)_4$[a]	40[e]	153–154	$C_{19}H_{23}NSO_3$	66.1	65.8	6.6	6.3
10A	$N(CH_2)_4O$[b]	92	159–160	$C_{19}H_{23}NSO_4$	63.2	62.9	6.4	6.4
11A	$N(CH_2)_5$[c]	57[f]	160–161	$C_{20}H_{25}NSO_3$[g]	66.9	67.2	7.0	7.1
12A	$N(CH_2)_4NCH_3$[d]	76	204–206 effer.	$C_{13}H_{19}N_2Cl\cdot HCl\cdot H_2O$[h]	53.2	53.3	7.5	7.4
9B	$N(CH_2)_4$[a]	95	203–204	$C_{25}H_{27}NSO_3$	71.2	70.8	6.4	6.4
10B	$N(CH_2)_4O$[b]	97	224–225	$C_{25}H_{27}NSO_4$	68.6	68.7	6.2	6.4
11B	$N(CH_2)_5$[c]	38[i]	237–238	$C_{26}H_{29}NSO_3$[j]	71.7	71.5	6.7	6.8
12B	$N(CH_2)_4NCH_3$[d]	41[k]	257–258	$C_{33}H_{37}N_2S_2O_6$	63.6	63.3	6.1	6.1

[a] Pyrrolidino. [b] Morpholino. [c] Piperidino. [d] 1-Methylpiperazinyl. [e] Recovered 57% of the unchanged base 5A. [f] Yield, 85% based on the reactant p-$CH_3C_6H_4SO_2Cl$ used. [g] Compound 11A. Calcd. for N: 3.9. Found: 3.7. [h] Calcd. for N: 9.6. Found: 9.4. Melts with decomposition at 269–270°. [i] Recovered 50% of the unreacted aminocarbinol 7B. [j] Compound 11B. Calcd. for N: 3.2. Found: 3.3. [k] Isolated as p-toluenesulfonic acid salt of quaternary tosylate using one equivalent of the reagent.

centrated. Crystallization from ether–pentane mixtures gave colorless prisms, m.p. 69–70°, in 92% yield.

Addition of ethanolic hydrogen chloride solution to the base in ether gave a gummy product. Crystallization from methanol–acetone mixture with addition of ether to incipient turbidity gave needles, m.p. 199–200°.

2-Pyrrolidinomethyl-2′-hydroxymethyldiphenyl Hydrochloride (Compound 5B).—Nine grams of the amido acid, compound 1B, was reduced with 4 g. of lithium aluminum hydride by essentially the same procedure described for compound 8A. The oily product from reduction when distilled[7] at 114° under 48-μ pressure gave 84% of pure base. The hydrochloride salt also was prepared as described earlier.

Dihydroisoindoletetramethylene Ammonium Tosylate (Compound 9A).—A solution of 5.5 g. (0.029 mole) of the base, o-(pyrrolidinomethyl) benzyl alcohol, compound 5A, in 50 ml. of triethylamine was added to a solution of 2.1 g. (0.0013 mole) of p-toluenesulfonyl chloride in 50 ml. of dry triethylamine. On warming within a few minutes a voluminous precipitate appeared. After half an hour a heavy crystalline mass settled and the solution was clear. The solvent was removed *in vacuo* and the mixture was repeatedly triturated with ether. The crystalline product was subjected to vacuum sublimation when 1.5 g. of triethylamine hydrochloride was collected. The residue, on crystallization from methanol–acetone mixtures, gave needles, m.p. 153–154°, 4 g. in 40% yield.

The ether washings were extracted with 5% aqueous sodium hydroxide solution, dried over potassium carbonate, and concentrated. Crystallization from ether–pentane mixtures gave 3 g. of the starting base, b.p. 100° under 30-μ pressure.

Dihydro-5-dibenz[c,e]azepinespirotetramethylene Ammonium Tosylate (Compound 9B).—This was prepared from 12 g. (0.045 mole) of the base (compound 5B) and 10 g. of p-toluenesulfonyl chloride in 125 ml. of triethylamine by the same procedure as described for compound 9A, except for the following modification for the isolation of the intermediate tosyl ester hydrochloride.

After warming the mixture for 15 min., when the voluminous precipitate appeared, about 10 ml. of the suspension was taken out and repeatedly washed with ether. The precipitate was further triturated with ether when m.p. 170–171° was obtained. This was identified as o-pyrrolidinomethyl-o'-hydroxymethyldiphenyl-p-toluenesulfonate hydrochloride.

Anal. Calcd. for $C_{25}H_{27}NO_3S\cdot HCl$: C, 65.7; H, 6.1; Cl, 7.7. Found: C, 65.4; H, 6.6; Cl, 7.8.

This material was next warmed in triethylamine for an additional half hour. The cyclic product was identical with that obtained from the main bulk of the reaction mixture. The mixture melting point was undepressed. The combined yield was 95%.

1-Hydroxymethyl-8-piperidinomethylnaphthalene Hydrochloride.—A mixture of 20 g. (0.1 mole) of 1,8-naphthalic anhydride and 30 g. of piperidine together with 0.5 g. of p-toluenesulfonic acid was refluxed for 16 hr. On removal of the excess amine *in vacuo*, the solid product was triturated with ether.

The solid amido acid, 20 g., was added to a solution of 13 g. of lithium aluminum hydride in 2 l. of anhydrous ether. On working up the reaction mixture as before, a base, m.p. 150–151°, recrystallized from ether–pentane mixtures was obtained.

Anal. Calcd. for $C_{17}H_{21}NO$: C, 80.1; H, 8.23. Found: C, 80.0; H, 8.6.

Addition of ethanolic hydrochloric acid to 1 g. of the base in ether gave the salt. It was recrystallized from a methanol–ether mixture, m.p. 186–187°, with effervescence.

Anal. Calcd. for $C_{17}H_{21}NO\cdot HCl\cdot 1.5H_2O$: C, 64.0; H, 7.8. Found: C, 63.8; H, 7.6.

Spiro[1*H*-benz[d,e]isoquinoline-2(3H),1′-piperidinium]-p-toluenesulfonate.[9]—A solution of 4 g. of the base together with 3.2 g. of p-toluenesulfonyl chloride in 125 ml. of triethylamine was heated for 10 min. Working up the reaction mixture as before, 6.5 g. of the product, m.p. 196–197°, was obtained.

Anal. Calcd. for $C_{24}H_{27}NSO_3$: C, 70.4; H, 6.6; N, 3.4. Found: C, 70.3; H, 6.8; N, 3.3.

(9) The name was kindly suggested by D. F. Walker, Jr., of the Chemical Abstracts Service.