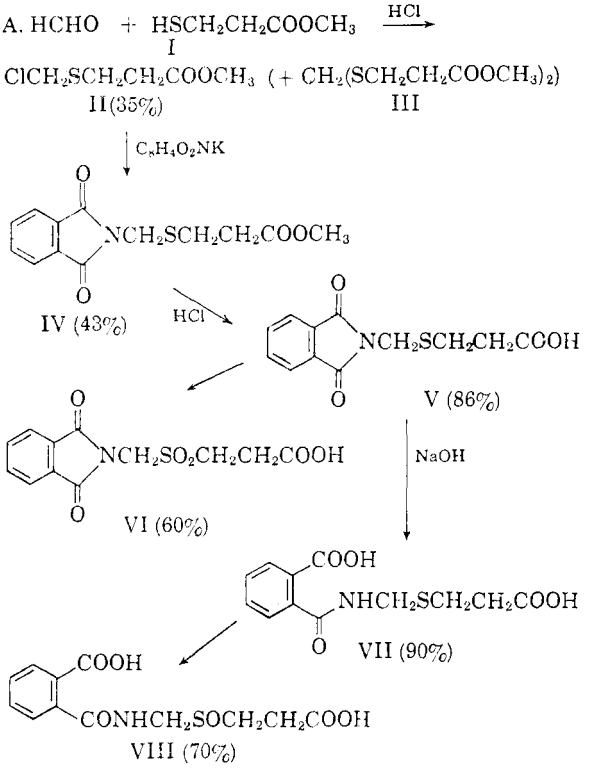
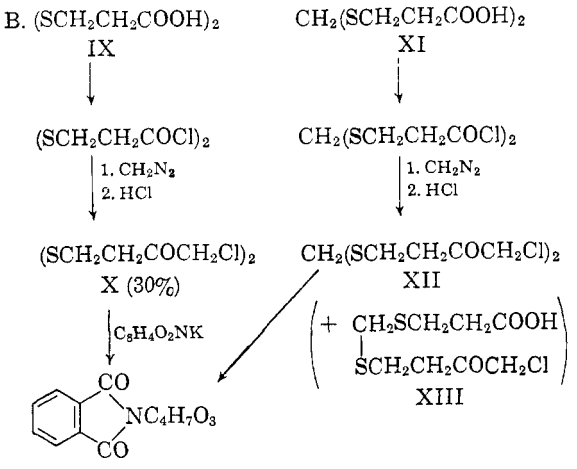
an effort to prepare δ-aminolevulinic acid analog B. These were patterned after the successful synthesis



of δ-aminolevulinic acid.[6] The effort proved abortive when it was found that both chloromethyl ketones X and XII, on reaction with phthalimide, produced the same sulfur-free compound, $C_{12}H_{11}O_5N$. The structure of this compound has not been established, but the infrared spectra show the phthalimido ring system to be present. The absence of a carboxyl group was indicated by titration and the infrared spectrum. The latter also suggest there are no free hydroxyl groups.



PHILADELPHIA 4, PA.

(6) A. Neuberger and J. J. Scott, *J. Chem. Soc.*, 1820 (1954).

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Cyclopropanes Derived from Diaryldiazomethanes. II. 3-Azabicyclo[3.1.0]-hexanes and Their Azaspiroquaternary Salts[1]

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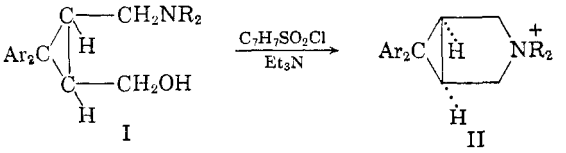
The 6,6-diaryl-3-azabicyclo[3.1.0]hexane ring system can be prepared by alternative routes: through addition of diaryldiazomethanes to *N*-substituted maleimides and citraconimides followed by reduction, and by cyclization of 1,1-diaryl-2-hydroxymethyl-3-*cis*-*t*-aminomethylcyclopropanes by the action of *p*-toluenesulfonyl chloride. The latter route affords access to *N*-spiroquaternary ammonium salts.

In the course of an investigation of the amino-alcohols of the formula I[5] several such compounds



were allowed to react with *p*-toluenesulfonyl chloride in the presence of tertiary bases (pyridine or preferably triethylamine). No sulfonic esters could be isolated; either the starting amino alcohol was recovered or the entire product had the properties of a quaternary salt. It seems reasonable to suppose that the sulfonic ester III is actually formed

(1) A portion of this material was presented by Dr. Mehta before the Organic Division of the American Chemical Society, Boston Meeting, April 1959.

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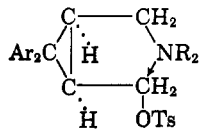
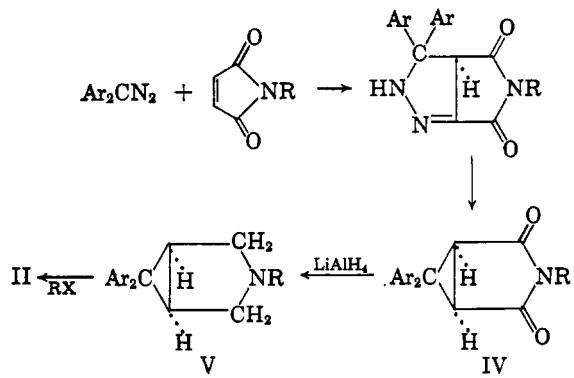
(5) R. Baltzly, N. B. Mehta, P. B. Russell, R. E. Brooks, E. M. Grivsky, and A. M. Steinberg, *J. Org. Chem.*, 26, 3669 (1961).

but that an intramolecular nucleophilic displacement then follows with great rapidity.



III

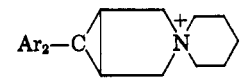
Certain quaternary salts of the nature of II can also be prepared by an independent synthesis starting with an *N*-substituted maleimide. This



V IV

route has been examined in part by Mustafa and his colleagues,[6] who reacted diphenyldiazomethane and 9-diazofluorene with *N*-aryl maleic and citraconic imides, obtaining the corresponding pyrazolines[7] and diketo azabicyclohexanes IV. For synthetic purposes isolation of the pyrazolines is not essential, and in a number of our reactions they were not isolated. Those obtained in pure form and characterized are shown in Table I. The 2,4-diketo-3-azabicyclo[3.1.0]hexanes of formula IV are presented in Table II. Reduction of these imides proceeded smoothly to give the bases of formula V, presented in Table III. Compound 35 (V. Ar = C_6H_5, R = H) was prepared by reduction with lithium aluminum hydride of the diketo imide compound 12 (IV. Ar = C_6H_5, R = $CONH_2$) and also by catalytic debenzylation of its *N*-benzyl analog, No. 39.

In contrast to the above debenzylation, which proceeded in a normal fashion, and to the reasonably facile reduction of one phenyl group in the cyclopropane amino alcohols[5] of the type of I, attempts to hydrogenate compounds 38 (V. Ar = C_6H_5, R = butyl) and 42 (V. Ar_2C = *o*-biphenylene, R = CH_3) were unsuccessful. Neither phenyl ring was reduced nor was the cyclopropane ring opened. This latter must be under considerable strain. It is apparent that the inaccessibility to the catalyst surface must be as important for catalytic hydrogenations as thermodynamic instability. It is not apparent why cyclization of I to a ring system such as V should render inaccessible to the catalyst the phenyl ring that is reducible in I.[5] However, the manner and extent in which the bond angles are distorted in the azabicyclohexane ring system of V is far from apparent. It would seem that study of this system by x-ray diffraction methods would be profitable.



VI

The tertiary bases of the 3-azabicyclo[3.1.0]-hexane series are most readily accessible by our second route through the diketo derivatives. Simple quaternary salts such as II (R = CH_3 or C_2H_5) can be prepared by either route. The first route, however, is vastly preferable for spiro quaternary salts such as VI. Three of the simple quaternary compounds (compounds 44, 45, and 48) were prepared by both routes. Specimens thus diversely prepared, after suitable manipulation to provide identical anions, proved to be identical.

The facile cyclization of the amino alcohols I to azabicyclo[3.1.0]hexane quaternary salts II also demonstrates the preservation of the *cis* character of the cyclopropane system in I through the various manipulations of the synthetic route.[5] Several of the steps involved might have permitted epimerization. That such did not occur is consistent with the strain theories propounded by H. C. Brown.[8]

Physiological activity of several types could be anticipated for various types of the compounds reported here. The cyclic imides IV are related to substances of known anticonvulsant activity. The tertiary amines and spiro quaternary salts could exhibit diverse types of activity. Some local anesthetic and analgesic action was detected in screening tests on these latter compounds, but these activities have so far not been sufficiently pronounced to appear of practical value.

EXPERIMENTAL[9]

5,5-Bis-p-tolylpyrazoline-3,4-dicarboxylic-N-n-butylimide (compound 9). To a solution of 4 g. (0.018 mole) of bis-*p*-tolyldiazomethane[5] in 500 ml. of anhydrous ether, 2.7 g. (0.016 mole) of *N*-*n*-butylmaleimide[10] was added. The solution was allowed to stand on the edge of the steam bath when a copious white precipitate of the product began to separate out. The solution was diluted with 100 ml. of *n*-pentane and left overnight at room temperature. The solu-

(6) A. Mustafa, S. M. A. D. Zayed, and S. Khattab, *J. Am. Chem. Soc.*, **78**, 145 (1956).

(7) Mustafa formulated his pyrazolines as Δ^1-unsaturated without presenting evidence therefore. The pyrazolines we have obtained from maleimide reduce permanganate in acetone at room temperature. For these, the Δ^2-formulation seems more acceptable. Compounds 2 and 5, Table I (from citraconimide), do not reduce permanganate and are probably Δ^1-pyrazolines.

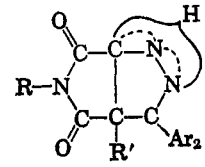
(8) H. C. Brown and M. Borkowski, *J. Am. Chem. Soc.*, **74**, 1894 (1952).

(9) All melting points are uncorrected.

(10) N. B. Mehta, A. P. Phillips, F. Fu Lui, and R. E. Brooks, *J. Org. Chem.*, **25**, 1012 (1960).

TABLE I

3,3-DIARYLPYRAZOLINE-4,5-DICARBOXYLICIMIDES

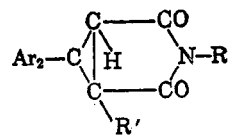


Compound	Ar	R′	R	M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	C_6H_5[a]	H	C_6H_5	150	$C_{23}H_{17}N_3O_2$	75.2	75.2	4.6	4.8
2	C_6H_5	CH_3	C_6H_5	138	$C_{24}H_{19}N_3O_2$	75.6	75.7	5.0	4.7
3	C_6H_5	H	C_6H_{11}	146	$C_{23}H_{23}N_3O_2$	74.0	73.7	6.2	6.0
4	C_6H_5	H	$CH_2C_6H_5$	134	$C_{24}H_{19}N_3O_2$	75.6	75.3	5.0	4.7
5	C_6H_5	CH_3	$CH_2C_6H_5$	124	$C_{25}H_{21}N_3O_2$	75.9	75.7	5.3	5.2
6	p-$CH_3OC_6H_4$	H	C_6H_5	130	$C_{25}H_{21}N_3O_4$	70.3	70.1	4.9	5.1
7	p-$CH_3C_6H_4$	H	CH_3	122	$C_{20}H_{19}N_3O_2$	72.1	71.9	5.7	5.9
8	p-$CH_3C_6H_4$	H	C_3H_7	122	$C_{22}H_{23}N_3O_2$	73.1	73.0	6.4	6.2
9	p-$CH_3C_6H_4$	H	C_4H_9	119	$C_{23}H_{25}N_3O_2$	73.6	73.4	6.7	6.3
10	p-$CH_3C_6H_4$	H	C_6H_5	146	$C_{25}H_{21}N_3O_2$	75.9	75.6	5.3	5.5
11	p-ClC_6H_4	H	C_6H_5	132	$C_{23}H_{15}Cl_2N_3O_2$	63.3	62.9	3.4	3.5

[a] Reported by A. Mustafa *et al.*, ref. 6, m.p. 143°.

TABLE II

2,4-DIOXO-3-AZABICYCLO[3.1.0]HEXANES



Compound	Ar	R′	R	M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
12	C_6H_5	H	$CONH_2$	184	$C_{18}H_{14}N_2O_3$	70.6	70.9	4.6	4.6
13	C_6H_5	H	CH_3	157	$C_{18}H_{15}NO_2$	78.0	77.8	5.4	5.6
14	C_6H_5	H	C_2H_5	194	$C_{19}H_{17}NO_2$	78.4	78.2	5.8	6.1
15	C_6H_5	H	C_3H_7	110	$C_{20}H_{19}NO_2$	78.7	78.6	6.2	5.9
16	C_6H_5	H	C_4H_9	136	$C_{21}H_{21}NO_2$	79.0	79.0	6.6	6.1
17	C_6H_5[a]	H	C_6H_5	172	$C_{23}H_{17}NO_2$	81.4	81.0	5.0	5.3
18	C_6H_5	CH_3	C_6H_5	186	$C_{24}H_{19}NO_2$	81.6	81.5	5.4	5.6
19	C_6H_5	H	C_6H_{11}	176	$C_{23}H_{23}NO_2$	80.0	80.0	6.7	6.5
20	C_6H_5	H	$CH_2C_6H_5$	193	$C_{24}H_{19}NO_2$	81.6	82.0	5.4	5.5
21	C_6H_5	CH_3	$CH_2C_6H_5$	135	$C_{25}H_{21}NO_2$	81.7	81.3	5.7	5.8
22	C_6H_5	CH_3	$(CH_2)_2N(C_2H_5)_2$	94	$C_{24}H_{28}N_2O_2$	76.6	76.7	7.4	7.1
23	p-$CH_3OC_6H_4$	H	CH_3	80	$C_{20}H_{19}NO_4$	71.2	71.0	5.6	5.3
24	p-$CH_3OC_6H_4$	H	C_6H_5	152	$C_{25}H_{21}NO_4$	75.2	75.5	5.3	5.2
25	p-$CH_3C_6H_4$	H	CH_3	136	$C_{20}H_{19}NO_2$	78.7	78.4	6.2	6.0
26	p-$CH_3C_6H_4$	H	C_3H_7	110	$C_{22}H_{23}NO_2$	79.3	79.2	6.9	6.8
27	p-$CH_3C_6H_4$	H	C_4H_9	78	$C_{23}H_{25}NO_2$	79.5	79.5	7.2	7.3
28	p-$CH_3C_6H_4$	H	C_6H_5	159	$C_{25}H_{21}NO_2$	81.7	81.6	5.7	5.8
29	p-ClC_6H_4[b]	H	C_2H_5	176	$C_{19}H_{15}Cl_2NO_2$	63.3	63.5	4.2	4.5
30	p-ClC_6H_4	H	$CH_2C_6H_5$	213	$C_{24}H_{17}Cl_2NO_2$	68.2	68.3	4.0	3.8
31	$C_{13}H_8$[c]	H	$CONH_2$	332	$C_{18}H_{12}N_2O_3$	71.1	70.8	3.9	3.8
32	$C_{13}H_8$[c]	H	CH_3	268	$C_{18}H_{13}NO_2$	78.5	78.6	4.7	4.7
33	$C_{13}H_8$[c]	H	C_2H_5	204	$C_{19}H_{15}NO_2$	78.9	79.0	5.2	5.2
34	$C_{13}H_8$[c,d]	H	C_6H_5	214	$C_{23}H_{15}NO_2$	81.9	81.6	4.5	4.3

[a] Reported by A. Mustafa *et al.*, ref. 6, m.p. 178°. [b] Nitrogen Calcd.: 3.9. Found: 3.8. Chlorine Calcd.: 19.7. Found: 19.1. [c] Ar_2C = *o*-biphenylene. [d] Reported by A. Mustafa *et al.*, ref. 6, m.p. 193°.

tion was filtered, and the precipitate was washed repeatedly with pentane, 6 g. (90%), m.p. 119° dec. An acetone solution decolorized permanganate immediately. Others in the series shown in Table I were prepared by essentially similar procedures.

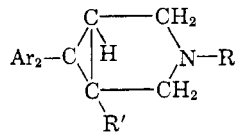
6,6-Bis-p-tolyl-2,4-dioxo-3-n-butyl-3-azabicyclo[3.1.0]-hexane (compound 27). Six grams of the pyrazoline (compound 9) was dissolved in 50 ml. of benzene and refluxed for 3 hr. It was concentrated to 15 ml. *in vacuo* and pentane was added. On cooling, 5.5 g. of thick prisms, m.p. 78°, was obtained.

Others[11] in the series shown in Table II were obtained by

(11) For compounds 12 and 31, *N*-carbamylmaleimide was obtained as a sample from Naugatuck Chemical Co., Naugatuck, Conn.

TABLE III

6,6-DIARYL-3-AZABICYCLO[3.1.0]HEXANES

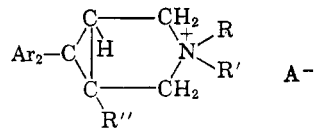


Compound	Ar	R′	R	M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
35	C_6H_5	H	H	101	$C_{17}H_{17}N$	86.9	86.6	7.2	7.4
				257	$C_{17}H_{17}N\cdot HCl$	75.1	75.0	6.6	6.4
36	C_6H_5	H	CH_3	66	$C_{18}H_{19}N$	86.7	86.2	7.6	7.8
37	C_6H_5	H	C_2H_5	60	$C_{19}H_{21}N$	86.7	86.5	8.0	8.3
				98[a]	$C_{23}H_{27}NO_6\cdot H_2O$	64.0	64.1	6.7	6.8
38	C_6H_5	H	C_4H_9	43	$C_{21}H_{25}N$	86.6	86.3	8.6	8.3
39	C_6H_5	H	$CH_2C_6H_5$	240	$C_{24}H_{23}N\cdot HCl$	79.7	79.4	6.6	7.2
40	C_6H_5[b]	CH_3	$CH_2C_6H_5$	110	$C_{25}H_{25}N$	88.5	88.8	7.4	7.4
41	p-$CH_3C_6H_4$	H	C_4H_9	175	$C_{23}H_{29}N\cdot HCl$	77.6	77.3	8.4	8.3
42	$C_{13}H_8$[c]	H	CH_3	145	$C_{18}H_{17}N$	87.4	86.9	6.9	6.6
43	$C_{13}H_8$[c]	H	C_2H_5	147	$C_{19}H_{19}N$	87.4	86.8	7.3	7.2
				262	$C_{19}H_{19}N\cdot HCl$	76.6	76.8	6.7	6.8

[a] Analyzed as tartrate monohydrate. [b] *Anal.* Nitrogen Calcd.: 4.13. Found: 4.18. [c] Ar_2C = *o*-Biphenylene.

TABLE IV

6,6-DIARYL-3-AZABICYCLO[3.1.0]HEXANES—QUATERNARY SALTS



Compound	Ar	R″	R / R′	M.P.	Formula[a]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
44	C_6H_5	H	$N(CH_3)_2$	249	$C_{19}H_{22}N\cdot I$	58.4	58.1	5.6	5.6
				180	$C_{19}H_{22}N\cdot C_7H_7SO_3$	71.6	71.6	6.7	6.9
				165	$C_{19}H_{22}N\cdot C_6H_2O_7N_3$[g]	60.9	61.1	4.9	4.7
45	C_6H_5	H	$N(C_2H_5)_2$	204	$C_{21}H_{26}N\cdot I$	60.1	60.0	6.2	6.3
				152	$C_{21}H_{26}N\cdot C_7H_7SO_3$	72.6	72.7	7.1	7.0
46	C_6H_5	H	$CH_3NC_4H_9$-n	220	$C_{22}H_{28}N\cdot I$	61.0	61.3	6.5	6.4
47	p-$CH_3C_6H_4$	H	$CH_3NC_3H_7$-n	238	$C_{23}H_{30}N\cdot I$	61.7	61.5	6.7	6.6
48	$C_{13}H_8$[b]	H	$N(CH_3)_2$	182	$C_{19}H_{20}N\cdot C_7H_7SO_3$	72.1	71.7	6.2	6.3
49	C_6H_5	H	$(CH_2)_4N$[c]	170	$C_{21}H_{24}N\cdot C_7H_7SO_3$	72.9	72.6	6.7	6.6
50	C_6H_5	H	$O(CH_2)_4N$[d]	220	$C_{21}H_{24}NO\cdot C_7H_7SO_3$	70.4	70.2	6.5	6.4
51	C_6H_5	H	$CH_3N(CH_2)_4N$[e]	285	$C_{22}H_{27}N_2\cdot C_7H_7SO_3\cdot H_2O$	68.5	68.7	7.1	6.7
52	C_6H_5	CH_3	$CH_3N(CH_2)_4N$[e]	209	$C_{23}H_{29}N_2\cdot C_7H_7SO_3$	71.4	71.2	7.1	7.3
53	p-$CH_3C_6H_4$	H	$(CH_2)_4N$[c]	170	$C_{23}H_{26}N\cdot C_7H_7SO_3\cdot 1/2H_2O$	72.3	71.7	7.2	7.3
54	p-$CH_3C_6H_4$	H	$O(CH_2)_4N$[d]	208	$C_{23}H_{26}NO\cdot C_7H_7SO_3$	71.3	71.2	6.9	6.9
55	$C_{13}H_8$[b]	H	$CH_3N(CH_2)_4N$[e]	280	$C_{22}H_{25}N_2\cdot Cl$	74.7	74.9	7.4	7.2
56	$C_{13}H_8$[b]	H	$(CH_2)_4N$[c]	195	$C_{21}H_{22}N\cdot C_7H_7SO_3\cdot 1/2H_2O$	71.8	71.5	6.4	6.3
57	$C_{13}H_8$[b]	CH_3	$(CH_2)_4N$[c]	219	$C_{22}H_{24}N\cdot C_7H_7SO_3$	73.6	73.2	6.6	6.6
58	$C_{13}H_8$[b]	H	$O(CH_2)_4N$[d]	231	$C_{21}H_{22}NO\cdot C_7H_7SO_3$	70.7	70.7	6.1	6.2
59	$C_{13}H_8$[b]	H	$(CH_2)_5N$[f]	248	$C_{22}H_{24}N\cdot C_7H_7SO_3$	73.6	73.2	6.6	6.2

[a] Inspection of the empirical formulas will show whether the anion is chloride, iodide, tosylate, or picrate. [b] Ar_2C = *o*-Biphenylene. [c] Pyrrolidino. [d] Morpholino. [e] *N′*-Methylpiperazino. [f] Piperidino. [g] Nitrogen, Calcd.: 11.4. Found: 11.3.

essentially similar procedures. The pyrazolines were decomposed thermally, usually when dissolved in boiling xylene.

6,6-o-Biphenylene-2,4-dioxo-3-methyl-3-azabicyclo[3.1.0]-hexane (compound 32). To a solution of 14 g. (0.073 mole) of 9-diazofluorene in 250 ml. of anhydrous ether, 9 g. (0.081 mole) of *N*-methylmaleimide was added; and the mixture was diluted with 1 l. of hexane. After 1 hr., 15.9 g. (79% yield) of white needles, m.p. 267–268°, separated out. This was recrystallized from benzene, m.p. 268°. Analysis shows it to be the azabicyclohexane rather than the corresponding pyrazoline.

1-Methyl-6,6-diphenyl-2,4-dioxo-3-(2′-diethylaminoethyl)-3-azabicyclo[3.1.0]hexane (compound 22). To 10 g. of 1,1-diphenyl-3-methylcyclopropane-2,3-*cis*-dicarboxylic acid anhydride,[5] 5 g. of anhydrous diethylaminoethylamine was added dropwise. After the initial exothermic reaction had subsided, the reaction mixture was heated at 100° for 1 hr. then for 3 additional hr. at 156°. On cooling overnight,

crystals were deposited. However, the reaction mixture was concentrated *in vacuo* to a viscous brown oil. It was crystallized from ether-pentane. Recrystallization gave a product of m.p. 94°, in 85% yield.

6,6-Bis-p-tolyl-3-n-butyl-3-azabicyclo[3.1.0]hexane (compound 41). The solid dioxo precursor, 3 g., (compound 27) was dropped portionwise through a powder addition funnel[12] into a rapidly stirred solution of 2 g. of lithium aluminum hydride in 250 ml. of anhydrous ether. After refluxing for 24 hr., it was decomposed by addition of water and then of 2 ml. of 10% sodium hydroxide solution. The clear ethereal layer was separated and dried over anhydrous potassium carbonate. The filtered ethereal solution was acidified with ethanolic hydrogen chloride solution, and the precipitated product was recrystallized from acetone-ether, m.p. 174–175°, yield 2.2 g.

Others in the series, shown in Table III, except compound 35, were prepared by the same procedure. The hydrochlorides of the bases were obtained by the addition of ethanolic hydrogen chloride solution to dry ethereal solutions of the bases.

6,6-Diphenyl-3-azabicyclo[3.1.0]hexane (compound 35). This was prepared by two methods. *Method A.* Six grams (0.016 mole) of 6,6-diphenyl-3-benzylazabicyclo[3.1.0]-hexane hydrochloride (compound 39) was dissolved in 50 ml. of methanol and shaken with 10% palladized charcoal under 2–3 atmospheres of hydrogen at room temperature. One equivalent of hydrogen over-pressure was consumed. The solution was filtered and evaporated to dryness *in vacuo.* The residue was dissolved in methanol-acetone and ether was added to incipient turbidity. There was obtained 4 g. of a crystalline product, melting at 256–257°. The analytical sample was dried at 100° for 3 hr. under 0.5μ pressure.

Method B. To a rapidly stirred, ethereal solution containing 20 g. of lithium aluminum hydride, 35 g. (0.114 mole) of 6,6-diphenyl-2,4-dioxo-3-*N*-carbamyl-3-azabicyclo[3.1.0] hexane (compound 12) was added portionwise from a solid powder addition funnel. The solution was stirred for 60 hr. at reflux temperature, decomposed by water, and by 5% sodium hydroxide. The ethereal layer was extracted with 400 ml. of 5% aqueous hydrochloric acid solution. The aqueous solution was basified and extracted with ether, and the ethereal extract was dried over anhydrous potassium carbonate. On addition of hexane, needles, m.p. 101–102°, separated out.

To the ethereal solution of the base, ethereal hydrochloric acid solution was added to *p*H 6. A colorless precipitate, changing to a yellow sticky mass was obtained; yield, 26 g. This was crystallized from acetone-ether, m.p. 250° dec. and had the composition of a hemihydrate. After drying for 3 hr. at 110° under 0.5 μ pressure, an anhydrous product m.p. 256° was obtained identical with that prepared by Method *A*.

Attempted reduction of 6,6-diphenyl-3-n-butyl-3-azabicyclo-[3.1.0]hexane (compound 38). Three grams (0.01 mole) of 6,6 - diphenyl - 3 - *n* - butyl - 3 - azabicyclo[3.1.0]hexane (compound 38) was dissolved in 50 ml. of glacial acetic acid and shaken with Adams' catalyst under 2–3 atmospheres of hydrogen at 60° for 2 hr. No apparent uptake of hydrogen other than by the catalyst was observed. Reduction of cyclohexane showed the catalyst was not poisoned. The starting compound was recovered unchanged.

A similar result was obtained with 6,6-*o*-biphenylene-3-methylazabicyclo[3.1.0]hexane (compound 42).

6,6-Diphenyl-3-methyl-3-azabicyclo[3.1.0]hexane methiodide (compound 44). Five grams of the base 1,1-diphenyl-2-hydroxymethyl - 3 - *cis* - dimethylaminomethylcyclopropane[5] was treated with 3.5 g. of *p*-toluenesulfonyl chloride in triethylamine, and the reaction mixture was worked up as described for compound 46 to yield 6 g. of 6,6-diphenyl-3,3-dimethyl-3-azabicyclo[3.1.0]hexane tosylate.

When to a clear solution of 3 g. of the azaspiro tosylate in 75 ml. of dry acetone, 1.2 g. of sodium iodide in 20 ml. of dry acetone was added, turbidity appeared. The solution was stirred at 40° for 24 hr. and filtered from a precipitate of 1 g. of sodium *p*-toluenesulfonate. The filtrate, on concentration and chilling, deposited crystals, m.p. 249°. The mixed melting point with the iodide obtained by direct quaternization of the bicyclic base (compound 36) with methyl iodide was undepressed.

In earlier experiments, tosylate from cyclization and iodide from quaternization of compound 35 were passed separately through columns of alkali-washed Amberlite IR-400, thus being converted to quaternary hydroxides. Neutralization of portions of the two eluates with picric acid afforded picrates that were found to be identical with each other.

6,6-Diphenyl-3,3-diethyl-3-azabicyclo[3.1.0]hexane tosylate (compound 45). To a solution of 12.5 g. of 1,1-diphenyl-2-hydroxymethyl-3-*cis*-diethylaminomethylcyclopropane[5] in 200 ml. of triethylamine, 10 g. of *p*-toluenesulfonyl chloride was added, and the mixture was refluxed on the steam bath for 4.5 hr. The solvent was removed *in vacuo,* and the residue triturated with ether to remove tosyl chloride and any amino alcohol remaining. The waxy mass was subjected to sublimation under 0.1 μ pressure at 90°; triethylamine hydrochloride sublimed out. The residue was dissolved in methanol and ether was added to incipient turbidity. Eight grams of crystalline product, m.p. 142°, was obtained, which had the composition of a monohydrate. After drying for 5 hr. at 110° under 0.5 μ pressure, an anhydrous product, m.p. 152° was obtained and was identical with that prepared by direct quaternization of the cyclic base with ethyl *p*-toluenesulfonate.

6,6-Diphenyl-3-n-butyl-3-azabicyclo[3.1.0]hexane methiodide (compound 46). To the solution of 2.5 g. of the base (compound 38) in 50 ml. of dry acetone, 15 ml. of methyl iodide was added and refluxed for 4 hr. Within 0.5 hr. crystals appeared. The solid was collected, washed with ether, and recrystallized from acetone-ether, m.p. 220°, yield 2 g.

6,6-o-Biphenylene-3,3-dimethyl-3-azabicyclo[3.1.0]hexane tosylate (compound 48). To 1 g. of the base (compound 42) dissolved in 50 ml. of methanol, 1 g. of methyl *p*-toluenesulfonate was added. The solution was refluxed on the steam bath for 10 min. and was left at room temperature overnight. Crystals were deposited and on addition of ether more separated. The solid was washed repeatedly with ether and recrystallized from hot acetone. One gram of glossy fine needles, m.p. 182°, was obtained.

The same compound was also prepared through the cyclization reaction of 1,1-*o*-biphenylene-2-hydroxymethyl-3-*cis*-dimethylaminomethylcyclopropane[5] with *p*-toluenesulfonyl chloride in triethylamine by the procedure described above for compound 45. The product melted at 59–60° and had the composition of a monohydrate. After drying for 3 hr. at 90° under 0.5 μ pressure, the anhydrous salt was obtained, m.p. 182°. The mixed melting point with that obtained above by direct quaternization of the cyclic base with methyl *p*-toluenesulfonate was undepressed.

1-Methyl-6,6-diphenyl 3-azabicyclo[3.1.0]hexane-3-spiro (3'-methylaza)pentamethyleneammonium tosylate (compound 53). To a solution of 1 g. of the amino alcohol, 1,1-diphenyl-2-(*N'* - methylpiperazinomethyl) - 3 - methyl - 3 - *cis* - hydroxymethylcyclopropane,[5] dissolved in 50 ml. of triethylamine, 1 g. of *p*-toluenesulfonyl chloride was added. The clear solution was warmed on the steam bath, and within 15 min. a flocculent precipitate appeared. The solution was refluxed for 1.25 hr., the solvent was removed *in vacuo,* and the residue was triturated with ether. The waxy mass was subjected to sublimation at 1.5 μ pressure and 95° to remove triethylamine hydrochloride. The residue was dissolved in acetone and on addition of ether to incipient turbidity, 0.9 g. (62%) of fine wooly needles, m.p. 209°, separated.

The other spiro quaternary salts shown in Table IV were

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prepared by methods essentially similar to those described above. Deviations in some cases were possible because of the physical properties of the products. The *p*-toluenesulfonates of the *o*-biphenylene derivatives, compounds 57, 59, and 60, are sparingly soluble in water. In these cases, high vacuum sublimation of triethylamine hydrochloride was not necessary; it was sufficient after the ether trituration stage, to dissolve the residue in hot water. These quaternary tosylates separated out on cooling substantially pure. In the case of compound 56, the residue from trituration with ether was partially dissolved in acetone. In this instance, the quaternary chloride separated.

It is also possible in most cases to remove the bulk of the triethylamine hydrochloride from the ether-triturated residue by extraction with acetone in which triethylamine hydrochloride is quite insoluble. In such cases the vacuum sublimation is still desirable but can be considerably abbreviated.

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[CONTRIBUTION FROM STERLING-WINTHROP RESEARCH INSTITUTE AND THE DEPARTMENT OF CHEMISTRY OF RENSSELAER POLYTECHNIC INSTITUTE]

Local Anesthetics. 3-Halo-4-dialkylaminoalkoxy-5-alkoxyanilines

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A number of 3-bromo- and 3-chloro-4-dialkylaminoalkoxy-5-alkoxyanilines were prepared. The lower members of the series are potent, short-acting local anesthetics. Intermediate 2-alkoxy-4-nitrophenols were made by the alkaline displacement of the 1-alkoxy group in 1,2-dialkoxy-4-nitrobenzenes.

We have previously reported from these laboratories a series of dialkylaminoalkyl 4-amino-2-alkoxybenzoates[2] which possess both a high degree of local anesthetic activity and a fair degree of antifibrillatory activity. Recent investigations in these areas have been directed toward the preparation of compounds with an intense but short-acting local anesthetic activity for application in the production of intradermal anesthesia.

The local anesthetic activity associated with alkyl 2-(dialkylaminoalkoxy)-4-aminobenzoates[3] and with basic aryl alkyl ethers[4] led us to prepare first some 4-dialkylaminoalkoxy-3-alkoxyanilines, which proved to be quite unstable (*cf.* Kaye *et al.*[5] and Herbst and Simonian[6]) even as the solid hydrochloride derivatives. The search for more stable compounds led to the preparation of a series of 3-halo-4-dialkylaminoalkoxy-5-alkoxyanilines.

The route to the 3-bromo- and 3-chloro-4-dialkylaminoalkoxy-5-alkoxyanilines was I–V (X = Br or Cl, n = 2 or 3, R = CH_3 to C_6H_{13}, NR_2' = various dialkylamino groups).

The route to 4-dialkylaminoalkoxy-3-alkoxyanilines was I–V (X = H). An alternate preparation of II (R = CH_3) was the nitrosation of guaiacol followed by oxidation.

The reduction of 1-(2-diethylaminoethoxy)-2-methoxy-4-nitrobenzene[7] gave the corresponding aniline which proved to be very unstable in air, even as the hydrochloride salt. As we felt that β-elimination might play a part in the observed instability of the 4-(2-dialkylaminoethoxy)-3-alkoxyanilines we attempted to increase stability by the use of a 4-(3-dialkylaminoalkoxy) side chain. The resulting series was only slightly more stable toward air oxidation.

In hope of improving stability by changing the orientation of the substituents, the preparation of 3-(2-diethylaminoethoxy)-4-alkoxyaniline (VI. R = CH_3, n-C_3H_7) and 2-(2-diethylaminoethoxy)-5-methoxyaniline hydrochlorides (VII) was next undertaken. The compound VI (R = CH_3) has been previously reported as an intermediate[8] with no mention of stability. The precursors of VI were prepared from the parent 2-alkoxyphenyl acetates. Nitration, saponification, and a Williamson ether synthesis gave the 1-(2-diethylaminoethoxy)-2-alkoxy-5-nitrobenzenes. The starting compounds for VII (Table V) were prepared in a sequence parallel to I–IV (X = H), utilizing 1,4-dialkoxy-2-

(1) Taken from material submitted by D. F. Page to the Department of Chemistry of Rensselaer Polytechnic Institute in partial fulfillment of the requirements for the Ph.D. degree.

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