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The Alkylation of 6-Aryl-6,7-diazaspiro[3.4]octane-5,8-diones

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The synthesis of 8-*tert*-aminoalkoxy-6-aryl-6,7-diazaspiro[3.4]oct-7-en-5-ones (I) and 6-*tert*-aminoalkyl-7-aryl-6,7-diazaspiro[3.4]octane-5,8-diones has been accomplished. Two synthetic methods are described, each of which yields principally one isomer or the other.

Büchi *et al.* (2) have described the alkylation of 4,4-disubstituted-1-phenylpyrazolidine-3,5-diones (I) in the presence of ethanolic potassium hydroxide as occurring on nitrogen at the 2-position (II). Use of this method in our laboratories has produced not only the *N*-alkylated pyrazolidine-3,5-diones (II), but *O*-alkylated derivatives (III) as well. However, when sodium hydride in diglyme was used as the condensing agent, *O*-alkylation predominated.

Apparently Büchi did not observe the formation of the *O*-alkyl isomer (IIIA) in the preparation of 1-(2-diethylaminoethyl)-4,4-diethyl-2-phenylpyrazolidine-3,5-dione (IIA). When we prepared IIA according to Büchi's procedure, we also obtained 3-(2-diethylaminoethoxy)-4,4-diethyl-1-phenyl-2-pyrazolin-5-one (IIIA) in 14% yield. The analogous reaction of 6-phenyl-6,7-diazaspiro[3.4]octane-5,8-dione (IV) with 2-chlorotriethylamine in the presence of ethanolic potassium hydroxide also afforded both isomers. The predominant product (51%) was 6-(2-diethylaminoethyl)-7-phenyl-6,7-diazaspiro[3.4]-octane-5,8-dione (V). The yield of 8-(2-diethylaminoethoxy)-6-phenyl-6,7-diazaspiro[3.4]oct-7-en-5-one (VI) was 17%.

In contrast to the results obtained using ethanolic potassium hydroxide, high yields of *O*-alkylated products were obtained when sodium hydride in diglyme was used as condensing agent. Less than 20% *N*-alkylation occurred, and in most preparations only a trace of the *N*-alkylated product was evident, as shown by weak carbonyl absorption at 5.7 μ in the infrared spectrum of the crude product. The derivatives prepared by this procedure are summarized in Tables IV and V.

Procedures of Büchi and co-workers and of Conrad and Zart (3) were used for the preparation of 6-aryl-6,7-diazaspiro[3.4]octane-5,8-dione intermediates (IV, Table III). This involved the cyclization of diethyl 1,1-cyclobutanedicarboxylate (VII) with a phenyl hydrazine derivative in sodium ethoxide solution.

The structure of the alkylated products was established by examination of the infrared and ultraviolet absorption spectra. Infrared absorption bands for the *O*-alkyl series at 5.8 μ (C=O) and at 6.12-6.13 μ (-C=N-) were in agreement with those reported by Michel and Matter (4) for 2-phenyl-3a-methyldihydropyrano[2,3-c]-7a-pyrazolin-3-one (VIII), which has infrared absorption at 5.84 μ and 6.12 μ. This compound is structurally similar to *O*-alkylated derivatives such as VI. Ebnöther and his associates (5) have also described a band at 6.18 μ as being characteristic of the imino grouping in other related *O*-alkyl and *O*-acyl derivatives of pyrazolidine-3,5-diones. The infrared spectra of *N*-alkylated derivatives such as II or V show two carbonyl bands at 5.7 μ and 5.8 μ and lack of absorption at 6.12 μ. These assignments for pyrazolidine-3,5-diones and related compounds are also in agreement with the literature (4, 5).

The ultraviolet absorption spectra are presented for representative *O*-alkyl and *N*-alkyl derivatives (Tables I and II). There is a bathochromic shift from 235-238 mμ to 239-245 mμ and an increase in ϵ values upon going from the *N*-alkyl to the *O*-alkyl series. A band of weak intensity appears at 274-282 mμ in the *O*-alkylated products, and the *N*-alkyl derivatives elicit a similar band of even weaker intensity at 275-285 mμ.

EXPERIMENTAL

Melting points are uncorrected. The infrared absorption spectra were determined in chloroform solution, mineral oil or potassium bromide discs. The ultraviolet absorption spectra were determined in methanol.

General Procedure A. 6-Aryl-6,7-diazaspiro[3.4]octane-5,8-diones (Table III).

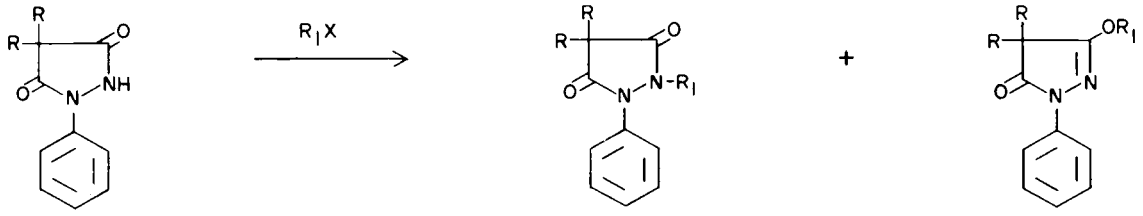
A mixture of 0.23 mole of diethyl 1,1-cyclobutanedicarboxylate and 0.23 mole of the appropriate phenylhydrazine was added with stirring and cooling to a solution of 0.45 mole of sodium ethoxide in absolute ethanol. The reaction mixture was heated at reflux temperature for 8 hours and evaporated to dryness. The residue was dissolved in 200 ml. of water and was extracted with ether. The aqueous phase was acidified with 90 ml. of 5 N hydrochloric acid. The yellow crystalline precipitate was filtered and washed with ether. The product was recrystallized from ethanol.

4,4-Diethyl-1-phenylpyrazolidine-3,5-dione.

This compound was prepared by the procedure of Conrad and Zart (3) in 46% yield, m.p. 112-113°. Conrad and Zart reported m.p. 114-115°.

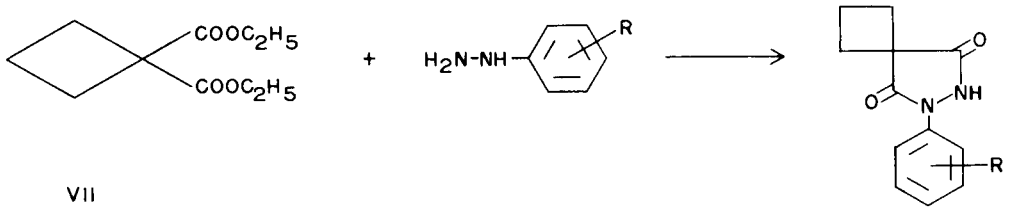
Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.2; H, 6.9; N, 12.1. Found: C, 66.8; H, 6.7; N, 12.1.

CHART

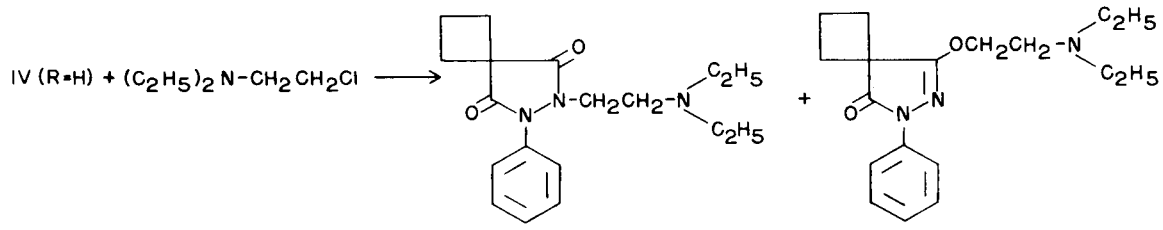


I II III

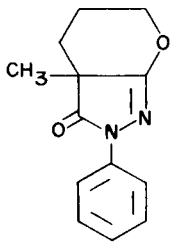
A: $R = C_2H_5$, $R_1 = C_2H_4N(C_2H_5)_2$



VII IV



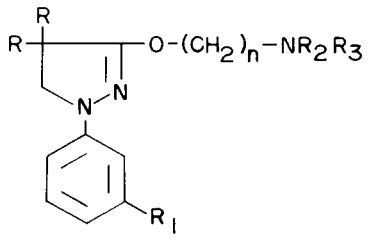
V VI



VIII

TABLE I

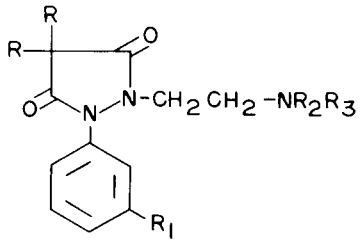
Ultraviolet Absorption Spectra of *O*-Alkylated Products



R, R	n	NR_2R_3	R_1	λ max mμ (ε)
$(C_2H_5)_2$	2	diethylamino	H	239 (15,250); 274 (6,400)
$-C_3H_6-$	2	dimethylamino	H	240 (15,900); 275 (4,230)
$-C_3H_6-$	2	diethylamino	H	241 (16,350); 276 (4,760)
$-C_3H_6-$	2	piperidino	Cl	245 (15,520); 280 (5,575)
$-C_3H_6-$	3	4-methyl-1-piperazinyl	Cl	245 (15,500); 282 (5,800)

TABLE II

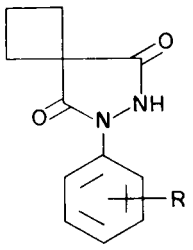
Ultraviolet Absorption Spectra of *N*-Alkylated Products



R, R	NR_2R_3	R_1	λ max mμ (ε)
$(C_2H_5)_2$	diethylamino	H	235 (8,850); 275 (2,400)
$-C_3H_6-$	diethylamino	H	235 (11,600); 280 (1,585)
$-C_3H_6-$	dimethylamino	Cl	238 (13,100); 285 (1,610)
$-C_3H_6-$	piperidino	Cl	238 (13,736); 285 (1,395)

TABLE III

6-Aryl-6, 7-diazaspiro[3.4]octane-5, 8-diones (a)

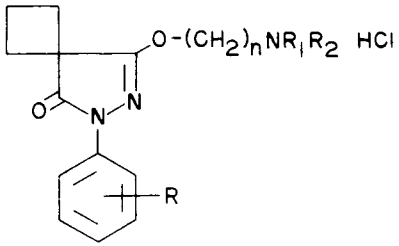


R	Yield, %	M.p., °C	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Chlorine Calcd.	Chlorine Found	Nitrogen Calcd.	Nitrogen Found
H	66	182-184	$C_{12}H_{12}N_2O_2$	66.7	66.4	5.6	5.9			13.0	13.2
m-Cl	42	134-136	$C_{12}H_{11}ClN_2O_2$	57.5	57.3	4.4	4.6	14.1	14.4	11.2	11.2
p-Cl	32	196-198	$C_{12}H_{11}ClN_2O_2$	57.5	57.4	4.4	4.7	14.1	14.4	11.2	11.3

(a) Compounds prepared by procedure A.

TABLE IV

8-*tert*-Aminoalkoxy-6-aryl-6,7-diazaspiro[3.4]oct-7-en-5-one Hydrochlorides (a)

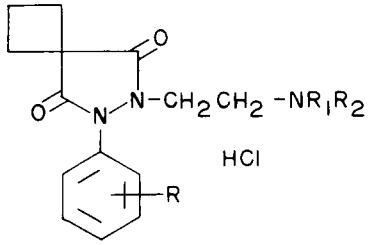


NR_1R_2	R	n	Yield, %	Recrystallization Solvent	Hydrochloride M.p.,°C	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Chlorine Calcd.	Chlorine Found	Nitrogen Calcd.	Nitrogen Found
dimethylamino	H	2	50	ethanol-ether	172-175	$C_{16}H_{22}ClN_3O_2$ (b)	59.3	59.2	6.8	6.8	11.0	10.8	13.0	12.8
dimethylamino	*m*-Cl	2	53	ethanol	194-196	$C_{16}H_{21}Cl_2N_3O_2$ (c)	53.6	53.8	5.9	6.1	19.8	20.0	11.7	11.9
dimethylamino	H	3	50	ethanol-ether	172-174	$C_{17}H_{24}ClN_3O_2$ (b)	60.4	60.0	7.2	7.4	10.5	10.2	12.4	12.3
diethylamino	H	2	17	acetone	188-189	$C_{18}H_{26}ClN_3O_2$ (d,e)	61.4	61.2	7.5	7.6	10.1	10.2	11.9	12.0
piperidino	H	2	76	ethanol	192-194	$C_{19}H_{26}ClN_3O_2$	62.7	62.1	7.2	7.0	9.7	9.5	11.6	11.6
piperidino	*m*-Cl	2	46	ethanol	192-194	$C_{19}H_{25}Cl_2N_3O_2$ (c)	57.3	56.9	6.3	6.3	17.8	17.8	10.6	10.6
piperidino	*p*-Cl	2	79	ethanol-ether	191-193	$C_{19}H_{25}Cl_2N_3O_2$	57.3	56.9	6.3	6.1	17.8	17.9	10.6	10.7
morpholino	*p*-Cl	2	70	ethanol	215-217	$C_{18}H_{23}Cl_2N_3O_3$ (b)	54.0	54.2	5.8	5.9	17.7	17.5	10.5	10.4
4-methyl-1-piperazinyl	H	3	47	ethanol	214-215	$C_{20}H_{30}Cl_2N_4O_2$ (f)	55.9	55.5	7.0	7.4	16.5	16.2	13.1	12.7
4-methyl-1-piperazinyl	*m*-Cl	3	43	ethanol	229-231	$C_{20}H_{29}Cl_3N_4O_2$ (f)	51.8	52.2	6.3	6.7	22.9	23.3	12.1	11.9
4-methyl-1-piperazinyl	*p*-Cl	3	61	ethanol	231-233	$C_{20}H_{29}Cl_3N_4O_2$ (b,f)	51.8	51.7	6.3	6.4	22.9	22.9	12.1	12.1

(a) Prepared by Procedure B. (b) Infrared spectrum showed trace amount of *N*-alkyl isomer in crude salt, which was removed by recrystallization. *N*-Alkyl isomer not isolated. (c) Separated from *N*-alkyl isomer by fractional recrystallization from ethanol. See Table V for *N*-alkyl isomer. (d) Prepared by Procedure C. (e) Separated from *N*-alkyl isomer by partition chromatography using a heptane 2-methoxyethanol solvent system and a diatomaceous silica column. Percent transmission was measured at 236 mμ. (f) Dihydrochloride.

TABLE V

6-*tert*-Aminoalkyl-7-aryl-6,7-diazaspiro[3.4]octane-5,8-dione Hydrochlorides



NR_1R_2	R	Yield, %	Recrystallization Solvent	Hydrochloride M.p.,°C	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Chlorine Calcd.	Chlorine Found	Nitrogen Calcd.	Nitrogen Found
dimethylamino	*m*-Cl	5	ethanol	180-182	$C_{16}H_{21}Cl_2N_3O_2$ (a,b)	53.6	53.3	5.9	6.1	19.8	19.5	11.7	11.4
diethylamino	H	51	acetone	164-165	$C_{18}H_{26}ClN_3O_2$ (c,d)	61.4	61.4	7.5	7.6	10.1	10.2	11.9	12.0
piperidino	*m*-Cl	9	ethanol	189-190	$C_{19}H_{25}Cl_2N_3O_2$ (a,b)	57.3	57.0	6.3	6.5	17.8	17.9	10.6	10.4

(a) Prepared by Procedure B. (b) Separated from *O*-alkyl isomer by fractional recrystallization from ethanol. (c) Prepared by Procedure C. (d) Separated from *O*-alkyl isomer by partition chromatography using a heptane 2-methoxyethanol solvent system and a diatomaceous silica column. Percent transmission was measured at 236 mμ.

General Procedure B. 8-*tert*-Aminoalkoxy-6-aryl-6,7-diazaspiro[3.4]-oct-7-en-5-ones (Table IV).

A solution of the 6-aryl-6,7-diazaspiro[3.4]octane-5,8-dione (0.01 mole) in 100 ml. of dry diglyme (diethylene glycol dimethyl ether) was added dropwise with stirring to a suspension of 600 mg. (0.012 mole) of 50% sodium hydride in mineral oil in 30 ml. of diglyme. When hydrogen ceased to evolve, a solution of 0.012 mole of the *tert*-aminoalkyl chloride in ether or diglyme was added. Stirring was continued at room temperature for 1-2 hours. The reaction mixture was heated at reflux temperature for 5-8 hours (any ether was first distilled off). The precipitate was filtered and the filtrate was concentrated under vacuum to remove most of the diglyme. The residue was treated with 25 ml. of water and extracted with ether. The ether extracts were dried over magnesium sulfate and concentrated to dryness. In some cases, where the infrared absorption spectrum of the crude product indicated the presence of the *N*-alkyl isomer, the products were separated by partition chromatography, as indicated in the tables. The products in ether solution were converted to the hydrochloride salts by the addition of ethanolic hydrogen chloride. The salts were recrystallized from ethanol or acetone.

General Procedure C. 6-*tert*-Aminoalkyl-7-aryl-6,7-diazaspiro[3.4]-octane-5,8-diones (Table V).

A reaction mixture consisting of 0.04 mole of the 6-aryl-6,7-diazaspiro[3.4]octane-5,8-dione, 0.05 mole of the *tert*-aminoalkyl chloride and 230 ml. of 1% ethanolic potassium hydroxide was allowed to stand for five days at room temperature. The precipitate was filtered. The filtrate was concentrated under vacuum on the water bath at 60°. Ice water (200 ml.) was added, and the mixture was extracted twice with 200 ml. portions of ether. The ether extracts were dried over magnesium sulfate and concentrated to dryness. The products were separated by partition chromatography. Hydrochlorides were prepared by the addition of ethanolic hydrogen chloride to the bases dissolved in ether. The salts were generally recrystallized from ethanol, ethyl acetate or acetone.

1-(2-Diethylaminoethyl)-4,4-diethyl-2-phenylpyrazolidine-3,5-dione (IIA) and 3-(2-Diethylaminoethoxy)-4,4-diethyl-1-phenyl-2-pyrazolin-5-one (IIIA).

The above mixture of isomers was obtained using 4,4-diethyl-1-phenylpyrazolidine-3,5-dione and 2-chlorotriethylamine according to procedures B and C. The products were separated by partition chromatography using a heptane 2-methoxyethanol solvent system and a diatomaceous silica column. Percent transmission was measured at 240 mμ. The products in ether solution were converted to hydrochloride salts by the addition of ethanolic hydrogen chloride. The hydrochloride of IIA was recrystallized from ethyl acetate. The hydrochloride of IIIA was recrystallized from acetone.

	% Yield IIA	Hydrochloride M.p.	% Yield IIIA	Hydrochloride M.p.
Proc. B	18	113-114°	54	165-166°
Proc. C	50	113-114°	14	164-165°

Proc. B. *Anal.* Calcd. for $C_{19}H_{29}N_3O_2 \cdot HCl$: C, 62.0; H, 8.2; Cl, 9.6; N, 11.4. Found (IIA): C, 61.8; H, 8.5; Cl, 9.6; N, 11.4. Found (IIIA): C, 61.7; H, 8.0; Cl, 9.6; N, 11.3.

Proc. C. Found (IIA): C, 61.4; H, 8.1; Cl, 9.6; N, 11.2. Found (IIIA): C, 62.0; N, 8.3; Cl, 9.6; N, 11.5.

The structures of the products obtained by both procedures were also corroborated by comparison of the infrared and ultraviolet absorption spectra.

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REFERENCES

(1) H. J. Brabander and W. B. Wright, Jr., U. S. Patent, 3,149,115 (1964).

(2) J. Büchi, J. Ammann, R. Lieberherr, and E. Eichenberger, *Helv. Chim. Acta*, 36, 75 (1953).

(3) M. Conrad and A. Zart, *Ber.*, 39, 2282 (1906).

(4) K. Michel and M. Matter, *Helv. Chim. Acta*, 44, 1025 (1961).

(5) A. Ebnöther, E. Jucker, E. Rissi, R. Steiner, R. Süess, and A. Vogel, *ibid.*, 42, 2013 (1959).

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