Twofold alkylations of ketone and aldehyde phenylhydrazones with methylene halides by means of alkali amides to form bis-*N*-derivatives[1]

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The phenylhydrazones of benzophenone, acetophenone, and benzaldehyde were converted by a molecular equivalent of an alkali amide in liquid ammonia to their mono-alkali derivatives, which underwent twofold alkylation with 1,3-dibromopropane or higher methylene halides or with α,α′-dichloro-*p*-xylene to form corresponding bis-*N*-derivatives. Two of the products were reduced by means of lithium in liquid ammonia to give corresponding substituted bis-hydrazines. These reactions furnish convenient methods of synthesis of such compounds.

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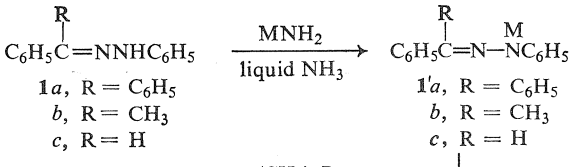
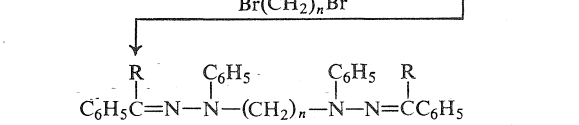
As an extension of a previous method for effecting certain *N*-alkylations of ketone and aldehyde phenylhydrazones with alkyl halides (1), we have now found that twofold *N*-alkylations of phenylhydrazones **1***a–c* can be accomplished with appropriate methylene bromides by means of alkali amides in liquid ammonia to form the bis-derivatives **2***a–f*, respectively. Similarly the intermediate alkali phenylhydrazones **1***a–b* underwent twofold alkylation with α,α′-dichloro-*p*-xylene to give the bis-derivatives **3***a–b*, respectively. The results are summarized in Tables I and II.

Table I shows that the yields of the analytically pure bis-derivatives **2***a–f* and **3***a–b* were quite satisfactory (48–81%). In certain cases the yields were slightly better with potassium amide than with sodium amide. The structures of the products were supported by analysis and absorption spectra (see Tables I and II). The most notable difference in the infrared (i.r.) spectra of the bis-derivatives from those of the starting phenylhydrazones is the lack of any absorption in the NH region. Otherwise, these spectra are similar to those of the starting phenylhydrazones except that the peaks appear at different frequencies. The nuclear magnetic resonance (n.m.r.) spectra of compounds **2***a–f* show an N—CH_2 triplet and those of **3***a–b* an N—CH_2 singlet. Their n.m.r. spectra are in complete agreement with the assigned structures.

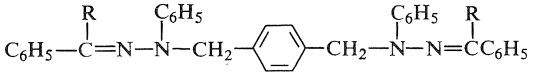


1*a*, R = C_6H_5
b, R = CH_3
c, R = H

1′*a*, R = C_6H_5
b, R = CH_3
c, R = H



2*a*, R = C_6H_5, $n = 3$
b, R = C_6H_5, $n = 4$
c, R = CH_3, $n = 4$
d, R = H, $n = 3$
e, R = H, $n = 4$
f, R = H, $n = 10$



3*a*, R = C_6H_5
b, R = CH_3

This method of synthesis would probably be suitable with, not only other phenylhydrazones, but also with other methylene bromides higher than 1,3-dibromopropane and with α,α′-dichloro-*o*-xylene (see Table I). However, the method failed with phenylhydrazone **1***a* and ethylene or methylene bromide or chloride with which the starting phenylhydrazone **1***a* was largely recovered. The results with the ethylene halides may be accounted for by β-elimination.

[1]This investigation was supported by United States Public Health Service Research Grant No. CA 04455 from the National Cancer Institute.

TABLE I

Twofold *N*-alkylations of phenylhydrazones with methylene halides by alkali amides in liquid ammonia to form bis-derivatives

Phenyl hydrazone	Methylene halide	bis-Derivative	Yield, % $NaNH_2$	Yield, % KNH_2	Melting point (°C)	Emperical formula	Elemental analysis: Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
1*a*	1,3-Dibromopropane	**2***a*	48	52	129–130*	$C_{41}H_{36}N_4$	84.21	6.21	9.58	84.41	6.09	9.40
1*a*	1,4-Dibromobutane	**2***b*	55	57	142–143†	$C_{42}H_{38}N_4$	84.24	6.40	9.36	84.04	6.41	9.28
1*b*	1,4-Dibromobutane	**2***c*	54	54	110–111*	$C_{32}H_{34}N_4$	80.97	7.22	11.81	80.93	7.18	11.69
1*c*	1,3-Dibromopropane	**2***d*	74	78	145.5–146.0*	$C_{29}H_{28}N_4$	80.52	6.53	12.95	80.34	6.46	12.74
1*c*	1,4-Dibromobutane	**2***e*	65	66	89.5–90.5*	$C_{30}H_{30}N_4$	80.68	6.77	12.55	80.50	6.88	12.44
1*c*	1,10-Dibromodecane	**2***f*	51	55	164–166*	$C_{36}H_{42}N_4$	81.47	7.98	10.56	81.31	7.91	10.71
1*a*	α,α′-Dichloro-*p*-xylene	**3***a*	—	81	158–159‡	$C_{46}H_{38}N_4$	85.41	5.92	8.66	85.15	5.81	8.73
1*b*	α,α′-Dichloro-*p*-xylene	**3***b*	—	73	145–146§	$C_{36}H_{34}N_4$	82.72	6.56	10.72	82.58	6.50	10.89

*Recrystallized from 95% ethanol.
†Recrystallized from methanol–hexane.
‡Recrystallized from hexane–benzene.
§Recrystallized from acetonitrile.

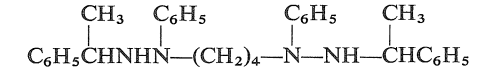
TABLE II

Infrared and nuclear magnetic resonance spectra of the bis-derivatives

bis-Derivative	C=N‡	γ*, cm^{-1} aromatic	C—N	Aromatic CH out-of-plane bend	Nuclear magnetic resonance data† (c.p.s. ± 1): Protons N—CH_2—	C—CH_2—C	C—CH_3	Aromatic
2*a*	1610	1595§, 1505	1250	755, 705	235 (t, 4.0)	122 (q, 2.0)		423–456 (m, 29.9)
2*b*	1620	1603, 1502	1270	760, 700	213 (t, 3.9)	106 (m, 4.0)		413–465 (m, 30.1)
2*c*	1610	1600, 1498	1300	765, 705	210 (t, 4.0)	107 (m, 4.0)	119 (s, 6.0)	405–473 (m, 20.0)
2*d*	1614	1600, 1500	1280	760, 701	236 (t, 4.1)	128 (q, 1.9)		420–460 (m, 22.0)
2*e*	1615	1598, 1500	1260	765, 690	230 (t, 4.1)	104 (m, 4.0)		414–470 (m, 22.1)
2*f*	1620	1605, 1505	1310	770, 705	228 (t, 4.1)	79–172 (m, 15.8)		415–458 (m, 21.7)
3*a*	1605	1595, 1495	1335	745, 690	272 (s, 4.0)			405–462 (m, 33.8)
3*b*	1615	1600, 1500	1345	755, 746, 685	296 (s, 3.9)		167 (s, 6.0)	428–474 (m, 24.1)

*All peaks are strong unless otherwise noted.
†Determined in deuteriochloroform; for n.m.r. descriptions see ref. 4.
‡Shoulders.
§Medium peak.

The bis-hydrazones **2***c* and **3***b* were reduced by means of lithium in liquid ammonia to form the corresponding substituted bis-hydrazines **4** and **5** in yields of 54 and 61%, respectively. The other bis-hydrazones could presumably be reduced similarly. This method has previously been employed for reduction of an α,β-unsaturated ketone (2).



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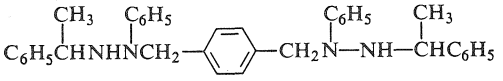

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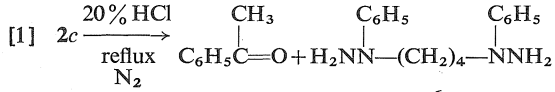
The structures of the bis-hydrazines **4** and **5** were supported by analysis and absorption spectra (see Experimental). The i.r. spectra of **4** and **5** lack the C=N peak observed in the spectra of starting bis-hydrazones **2***c* and **3***b* and have strong peaks for the NH and C—N groups. Although the n.m.r. spectrum of **4** is somewhat complicated by overlap of the methyl protons with the methylene protons and of the benzylic protons with the *N*-methylene protons, the n.m.r. spectrum for **5** shows the expected doublet for the methyl group and a quartet for the CH group adjacent to the methyl group.

The bis-hydrazones **2***c* and **3***b* were hydrolyzed with hot acid but the resulting bis-hydrazines or their acid salts appeared to be too unstable to isolate readily. For example, on refluxing a solution of **2***c* with 20% hydrochloric acid under nitrogen for 3 h, a dark tarry gum was obtained. That hydrolysis had occurred was shown by isolation of the ketone as its 2,4-dinitrophenylhydrazone (78%) and the bis-hydrazine **6** as its bis-benzaldehyde derivative **2***e* (12%) [eq. 1]:



[1]

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It may be concluded that the twofold alkylation of phenylhydrazones and subsequent reduction of the products furnish convenient methods for the synthesis of an apparently new class of bis-hydrazones and bis-hydrazines such as **2***a–f*, **3***a–b*, **4**, and **5**. The possible twofold condensation of a bis-hydrazine such as **6** with an aldehyde or ketone does not seem suitable, since **6** appears not readily available and too unstable for a satisfactory result (see above).

Experimental

Melting points, taken on a Thomas Hoover capillary melting point apparatus, are uncorrected. Infrared spectra were recorded on a Perkin–Elmer model 237 Infracord using samples prepared as potassium bromide pellets. Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer using deuteriochloroform solutions containing tetramethylsilane as an internal standard[2] Elemental analyses were performed by Paul Demoen, Janssen Pharmaceutical Laboratories, Beerse, Belgium, and M-H-W Laboratories, Garden City, Michigan.

The benzophenone phenylhydrazone (3), acetophenone phenylhydrazone (4), and the benzaldehyde phenylhydrazone (5) used in this study were prepared according to literature procedures. The acetophenone phenylhydrazone should be freshly prepared.

Twofold N-Alkylations of Phenylhydrazones

To a stirred suspension of 0.025 mole of sodium amide (6) or potassium amide (7) in 350 ml of commercial, anhydrous liquid ammonia was added a molecular equivalent of the phenylhydrazone **1***a*, **1***b*, or **1***c*. The solutions of the resulting alkali salt were colored blood-red, orange-tan, and brownish-yellow respectively. After 20 min, a solution of one half of a molecular equivalent of the appropriate dihalide in 15–20 ml of anhydrous ether was added during a 4–6 min period; the color of the solution was essentially discharged and a precipitate formed. After stirring for 45–60 min, a slight excess of a molecular equivalent of ammonium chloride was added. The ammonia was allowed to evaporate, and the residue was taken up in ether and water. The layers were separated and the aqueous layer was washed twice with 100 ml of ether. The ether layers were combined and dried ($MgSO_4$) and the solvent was removed. The residue was recrystallized from an appropriate solvent. The results are summarized in Tables I and II.

Reduction of bis-Derivative 2c

To a stirred, blue solution of 0.7 g (0.1 mole) of lithium in 250 ml of commercial, anhydrous liquid ammonia was added 2.30 g (0.005 mole) of **2***c* in 100 ml of dry THF (freshly distilled from lithium aluminium hydride) during a 10 min period. After 1 h, the color of the solution had changed to a darker blue. A slight excess of ammonium chloride was then added in small equal portions during a 20 min period. The ammonia was evaporated and the reaction mixture was worked up to give a yellowish solid which was recrystallized from ethanol to give 1.43 g (54%) of hydrazine **4** (yellowish crystals), m.p. 143–144°; i.r. 3420 cm^{-1} (NH), 1600 and 1500 cm^{-1} (aromatic), 1265 and 1335 cm^{-1} (C—N), 760 and 700 cm^{-1} (out-of-plane CH bend); n.m.r. ($CDCl_3$)

[2]In n.m.r. descriptions, s = singlet, d = doublet, t = triplet, qt = quartet, q = quintet, m = multiplet, b = broad.

105–129 c.p.s. (m, 10.0), 205–224 c.p.s. (m, 6.0), 284 c.p.s. (b, 1.8), 420–466 c.p.s. (m, 20.4).

Anal. Calcd. for $C_{32}H_{38}N_4$: C, 80.29; H, 8.00; N, 11.71. Found: C, 80.42; H, 7.93; N, 11.58.

Reduction of bis-Derivative 3b

This reaction was effected essentially as described above for **2c** to give, after recrystallization from methanol–acetonitrile, 1.60 g (61%) of hydrazine **5** (tan crystals), m.p. 126–127°; i.r. 3440 cm^{-1} (NH), 1603 and 1505 cm^{-1} (aromatic), 1270 and 1315 cm^{-1} (C—N), 765 and 690 cm^{-1} (out-of-plane CH bend); n.m.r. ($CDCl_3$) 124 c.p.s. (d, 6.0, $J = 9$), 215 c.p.s. (qt, 2.0, $J = 9$), 290 c.p.s. (s, 4.1), 355 c.p.s. (b, 2.1), 432–476 c.p.s. (m, 24.0).

Anal. Calcd. for $C_{36}H_{38}N_4$: C, 82.09; H, 7.27; N, 10.64. Found: C, 81.91; H, 7.32; N, 10.39.

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Steroid derivatives of cysteamine and cysteine

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A number of androstenone, estrone, and pregnenone derivatives of cysteamine have been prepared by reacting the steroid amines with ethylene monothiolcarbonate. The amides of androstenone carboxylic acid with mercaptoethylamine and cysteine have also been prepared.

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The only compounds which have shown any promise in affording protection against radiation in the animal body are cysteamine (2-mercaptoethylamine) and its simple derivatives (1). Cysteine, which was one of the first compounds reported to show radiation protection, is less effective (2). However, these compounds are relatively toxic and are also easily metabolized and eliminated from the body. The object of this work was to prepare derivatives which might be less toxic and less readily metabolized, by joining cysteamine and cysteine to a steroid molecule, while still leaving the mercapto group free, since this is essential for radiation protection. The following derivatives of cysteamine have been prepared: *N*-(2-mercaptoethyl)-3-ketopregn-4-en-20β-yl amine (**1**), *N*-(2-mercaptoethyl)-3-keto-androst-4-en-17β-yl amine (**2**), *N*-(2-mercaptoethyl)estra-1,3,5(10)-trien-3-ol-17β-yl amine (**3**), and *N*-(2-mercaptoethyl)-3-ketoandrost-4-ene 17β-carboxamide (**4**). A derivative of cysteine, *N*-(3-ketoandrost-4-ene 17β-carboxyl)cysteine (**5**), has also been synthesized.

The condensation of pregn-5-en-3-ol-20-amine with an excess of ethylene monothiolcarbonate gave a good yield of *N*-mercaptoethylpregn-5-en-3-ol-20β-yl amine. Although condensations with ethylene monothiolcarbonate are usually carried out (3, 4) with an excess of amine to avoid di-substitution, no *N,N*-dimercaptoethyl derivative was formed in the present case. This same compound was formed by using one equivalent of ethyl 2-mercaptoethylcarbonate (4). An Oppenauer oxidation of *N*-(2-mercaptoethyl)pregn-5-en-3-ol-20-yl amine under standard conditions gave *N*-(2-mercaptoethyl)-3-ketopregn-4-en-20β-yl amine (**1**), without oxidizing the mercapto group, although the yield was low. The molecular weight indicated that the compound was still in the free mercapto form.

As an alternative route pregn-5-en-3-ol-20β-yl amine was oxidized with chromium trioxide in pyridine (5) to 3-ketopregn-5-en-20β-yl amine, which was obtained in an impure state and in low yield, apparently due to the formation of chromium complexes. Oxidation of the corre-