C-Alkylations of Ketone or Aldehyde Phenylhydrazones, Oximes, and Azines Having α Hydrogen through 1,4- or 1,6-Dianions[1]

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Abstract: The phenylhydrazones of acetophenone, phenylacetaldehyde, and deoxybenzoin were converted by 2 equiv of potassium amide in liquid ammonia to 1,4-dipotassio salts, which were C-alkylated or C,N-dialkylated with benzyl chloride or *n*-butyl bromide. The dipotassio salt of acetophenone phenylhydrazone underwent coupling with 2,3-dibromo-2,3-dimethylbutane and twofold alkylation with 1,4-dibromobutane to form bishydrazones. Deoxybenzoin oxime was similarly converted to its dipotassio salt, which was C-benzylated with benzyl chloride. Acetophenone oxime was converted by 2 equiv of *n*-butyllithium to the 1,4-dilithio salt, which underwent C-benzylation with benzyl chloride, coupling with 2,3-dibromo-2,3-dimethylbutane, and twofold alkylation with 1,4-dibromobutane to form corresponding mono- or bisoximes. Acetophenone azine was converted by 2 equiv of *n*-butyllithium to the 1,6-dilithio salt, which was dibenzylated with benzyl chloride and cyclized by means of 2,3-dibromo-2,3-dimethylbutane; the latter reaction formed a dihydropyridazine, which was aromatized to give a pyridazine. A mixed azine was similarly cyclized and aromatized. Several of these reactions are useful in synthesis.

Dianions of active hydrogen compounds having the two negative charges in resonance with the same carbonyl or other activating group are of particular interest, since the anionic portion arising through the secondary ionization is much more nucleophilic than that from the primary ionization. Consequently, alkylation can be effected at the secondary site to the practical exclusion of alkylation at the primary site. Such preferential alkylation has previously been accomplished at the secondary sites of several 1,3-dianions, for example, at the relatively nucleophilic terminal positions of 1,3-dipotassioacetylacetone (**1**)[2] and 1,3-dilithioacetanilide (**2**),[3] which were prepared by means of 2 equiv of potassium amide in liquid ammonia and 2 equiv of *n*-butyllithium in ether, respectively.

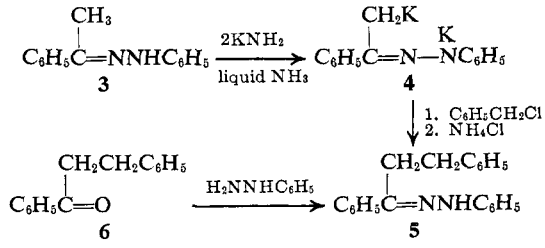
$KCH_2COCHCOCH_3$ (K) — **1**

$LiCH_2CONC_6H_5$ (Li) — **2**

Preferential alkylation has now been realized at the secondary site of 1,4- or 1,6-dianions of certain ketone or aldehyde phenylhydrazones, oximes, and azines having α hydrogen; these dianions were prepared by means of potassium amide or *n*-butyllithium.

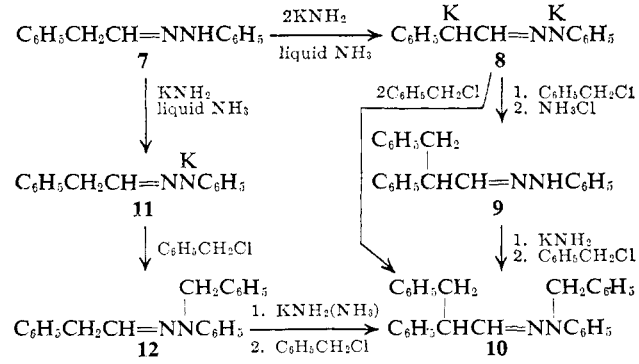
Results with Phenylhydrazones. Acetophenone phenylhydrazone has recently been N-alkylated with benzyl chloride through the monopotassio salt of the phenylhydrazone, which was prepared by means of a molecular equivalent of potassium amide in liquid ammonia.[4] This phenylhydrazone (**3**) has now been C-alkylated (at the methyl group) with benzyl chloride through the 1,4-dipotassio salt **4**, which was prepared with 2 equiv of this reagent. The product was **5**, which was independently synthesized from ketone **6** and phenylhydrazine (Scheme I).

Scheme I



Similarly, phenylacetaldehyde phenylhydrazone (**7**) was converted to its 1,4-dipotassio salt **8**, which was C-benzylated to form **9** and C,N-dibenzylated to give **10**. Also, **10** was prepared by N-benzylation of **9**, and by N-benzylation of **7** through monopotassio salt **11** followed by C-benzylation of the resulting **12** (Scheme II).

Scheme II



Moreover, dipotassio salt **8** was C,N-dialkylated with two different halides to form mixed dialkyl derivatives without isolation of the intermediate C-alkyl derivative. Thus, **8** was treated with 1 equiv of benzyl chloride followed by 1 of *n*-butyl bromide, and with 1 equiv of *n*-butyl bromide followed by 1 of benzyl chloride, to form **13** and **14**, respectively (Scheme III).

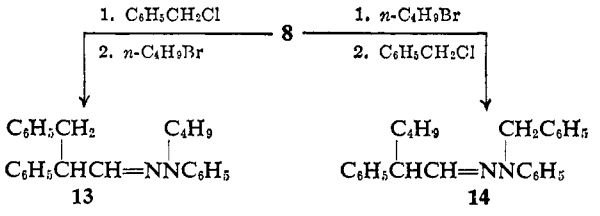
(1) (a) Supported by the Petroleum Research Fund administered by the American Chemical Society and by the National Science Foundation. (b) For a preliminary communication on part of this work, see F. E. Henoch, K. G. Hampton, and C. R. Hauser, *J. Am. Chem. Soc.*, **89**, 463 (1967).

(2) C. R. Hauser and T. M. Harris, *ibid.*, **80**, 6360 (1958).

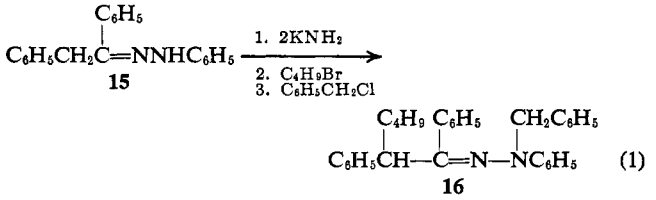
(3) R. L. Gay and C. R. Hauser, *ibid.*, **89**, 1647 (1967).

(4) W. G. Kenyon and C. R. Hauser, *J. Org. Chem.*, **30**, 292 (1965).

Scheme III



Likewise, deoxybenzoin phenylhydrazone (**15**) was converted to its 1,4-dipotassio salt which was C,N-dialkylated with *n*-butyl bromide followed by benzyl chloride to form the mixed dialkyl derivative **16** (eq 1).

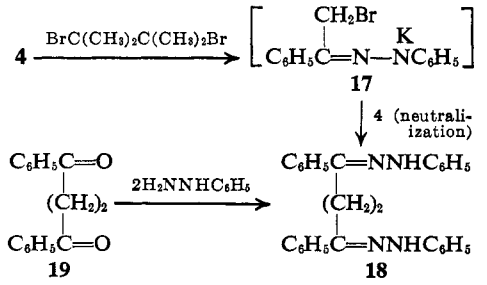


(1)

The yields obtained in these C-monoalkylations and C,N-dialkylations of dipotassiophenylhydrazones were good (54–78%). The carbanionic center of each dipotassio salt was sufficiently more nucleophilic than the nitrogen anionic center that C-alkylation occurred preferentially on treatment with 1 equiv (or slightly less) of the benzyl or *n*-butyl halide; thus, the crude C-alkylation products were indicated by tlc to be uncontaminated with the N-alkyl derivative. Also, the mixed dialkyl derivatives were indicated to be pure by tlc. A rough measurement of the relative nucleophilicities of dipotassio salt **8** and monopotassio salt **11** (see Scheme II) was obtained by observance of the time required to discharge the colors of these salts on adding 1 equiv of benzyl chloride. Thus, the dark red color of **8** was discharged almost immediately whereas the orange-brown color of **11** disappeared only after 20–30 min.

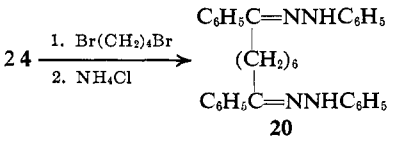
On turning to reactions of a dipotassiophenylhydrazone with certain dihalides, dipotassio salt **4** was found to undergo coupling with 2,3-dibromo-2,3-dimethylbutane to form **18** in 64% yield. Presumably dipotassio salt **4** underwent displacement on halogen with the dibromide to form the bromo intermediate **17** which then alkylated unchanged **4**, 2,3-dimethyl-2-butene being a by-product;[5] coupled product **18** was independently synthesized from diketone **19** (Scheme IV).

Scheme IV



(5) See W. G. Kofron and C. R. Hauser, *J. Am. Chem. Soc.*, **90**, 4126 (1968); also see K. Ziegler and B. Schnell, *Ann.*, **437**, 227 (1924).

Dipotassio salt **4** underwent twofold alkylation with 1,4-dibromobutane to form **20** (eq 2). The yield of **20** was only 24% when the stoichiometric amounts of 2 equiv of dipotassio salt **4** to one of the dibromide were used, and much polymeric material was produced. However, the yield of **20** was increased to 62% when 4 equiv of dipotassio salt **4** to one of the dibromide was employed. The polymeric material apparently arose under the former condition because, toward the end of the reaction, the monopotassio salt of the intermediate monobromide and, especially, the dipotassio salt of **20** competed favorably with the dipotassio salt **4** for the 1,4-dibromobutane and for the intermediate monobromide.

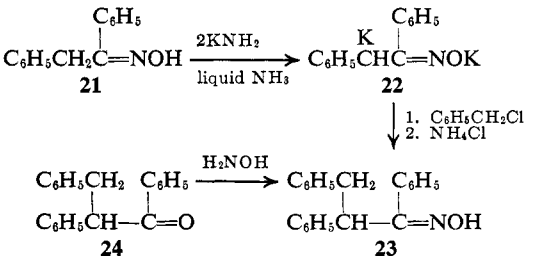


(2)

Although the method would presumably be suitable with 1,3-dibromopropane and higher methylene dihalides, dipotassio salt **4** failed to condense appreciably with ethylene chloride, and the starting acetophenone phenylhydrazone (**3**) was recovered; possibly the dihalide underwent β elimination. Also, the method failed with dipotassio salt **4** and methylene bromide, with which tarry material was produced. Similar results have previously been obtained with dialkali β-diketones such as **1** and methylene dihalides.[6]

Results with Oximes. Deoxybenzoin oxime (**21**) was converted by 2 equiv of potassium amide in liquid ammonia to 1,4-dipotassio salt **22**, which underwent C-benzylation with benzyl chloride to form **23** in 46% yield; this product was independently synthesized from ketone **24** (Scheme V).

Scheme V



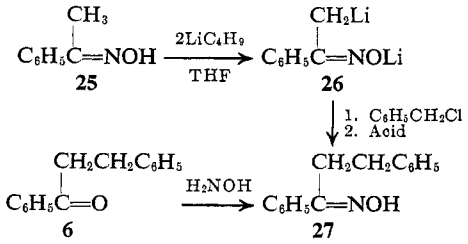
However, similar treatment of acetophenone oxime with 2 equiv of potassium amide, followed by benzyl chloride, failed to afford satisfactorily the C-benzyl derivative of the oxime; instead, stilbene was obtained. Evidently, sufficient potassium amide was present in equilibrium with the intermediate monoanion of the oxime to convert the halide to stilbene.[7]

Acetophenone oxime (**25**) was converted to its 1,4-dilithio salt **26** by means of 2 equiv of the stronger base, *n*-butyllithium, as evidenced by C-benzylation with benzyl chloride to form **27** in 68% yield; this product was independently synthesized from benzylacetophenone (**6**) (Scheme VI).

(6) K. G. Hampton, R. J. Light, and C. R. Hauser, *J. Org. Chem.*, **30**, 1413 (1965).

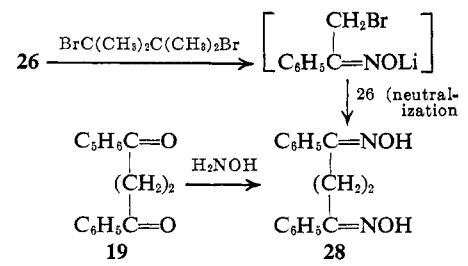
(7) See C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *J. Am. Chem. Soc.*, **78**, 1653 (1956).

Scheme VI



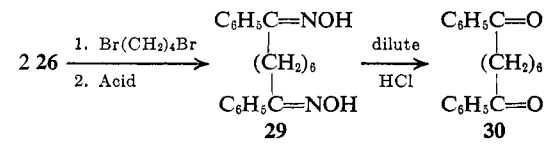
Dilithioacetophenone oxime (**26**) underwent coupling with 2,3-dibromo-2,3-dimethylbutane to form **28** in 58% yield.[5] This product was independently synthesized from 1,4-diphenyl-1,4-butanedione (**19**) as described previously[8] (Scheme VII).

Scheme VII



Dilithioacetophenone oxime (**26**) underwent twofold alkylation with 1,4-dibromobutane to give **29**. When the ratio of **26** to the dibromide was 2:1 the yield of **29** was only 32%, but when the ratio was increased to 4:1 the yield was increased to 66%. The product was hydrolyzed to afford diketone **30** in 74% yield (Scheme VIII). Bisoxime **29** has previously been prepared from

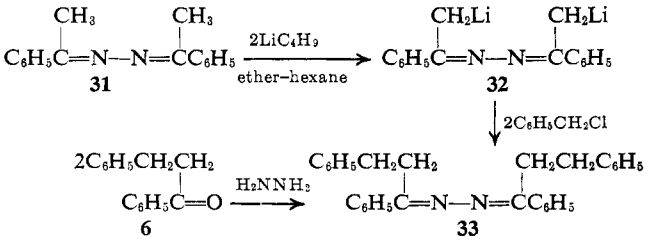
Scheme VIII



diketone **30** and hydroxylamine.[9]

Results with Azines. Acetophenone azine (**31**) was converted to its 1,6-dilithio salt **32** by 2 equiv of *n*-butyllithium in ether–hexane, as evidenced by dibenzylation with benzyl chloride to form **33** in 56% yield; this product was independently synthesized from benzylacetophenone (**6**) (Scheme IX).

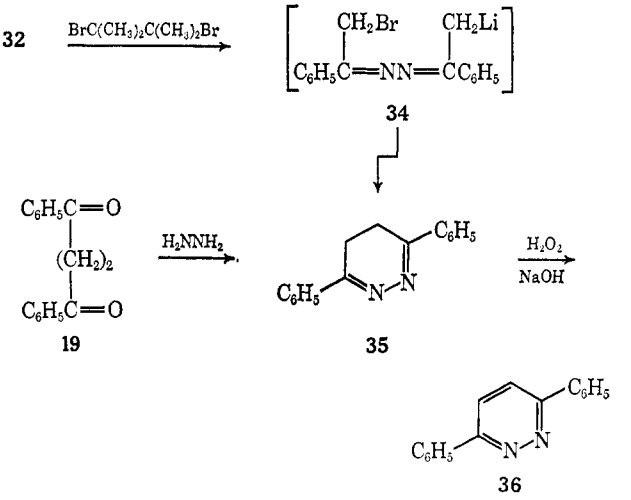
Scheme IX



Incidentally, azine **31** failed to undergo appreciable dibenzylation on treatment with 2 equiv of potassium amide in liquid ammonia, followed by 2 of benzyl chloride; instead stilbene was produced.[7] However, dibenzyl derivative **33** was obtained in 32% yield along with stilbene when the liquid ammonia was replaced by tetrahydrofuran before adding the halide.

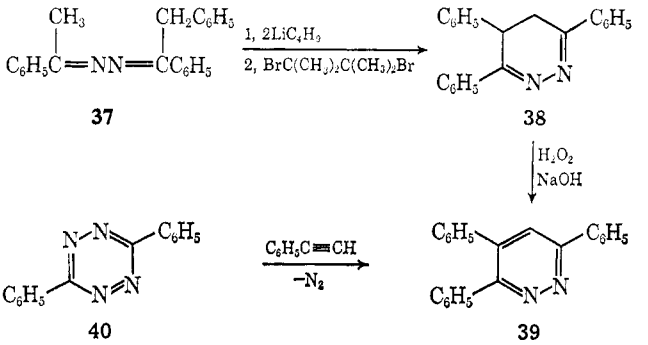
Dilithio salt **32** was cyclized with 2,3-dibromo-2,3-dimethylbutane to form dihydropyridazine **35** in 40% yield; presumably bromo lithio salt **34** was an intermediate, and 2,3-dimethyl-2-butene was a by-product.[5] Cyclic product **35** was independently synthesized from 1,4-diphenyl-1,4-butanedione (**19**) and hydrazine, and both samples of **35** were oxidized (aromatized) to afford pyridazine **36** in high yield (Scheme X).

Scheme X



Similarly, the mixed azine **37** was cyclized to form **38** which was aromatized to give **39** in an over-all yield of 78%. Previously,[10] **39** has been prepared from tetrazine **40** and phenylacetylene (Scheme XI).

Scheme XI

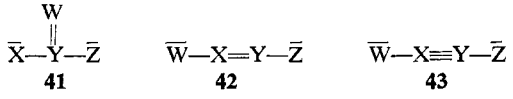


Discussion

These results represent a significant advance in our studies of resonance dianions. In contrast to earlier dianions of the 1,3 type (for example, **1** and **2**) in which the activating double bond protrudes from the 1,3 system as in general formula **41**, the present 1,4 type of dianion contains the activating double bond within the 1,4 system as in general formula **42**. Similarly, the present 1,6 type of dianion contains two such double bonds within the 1,6 system. Also, preparation of

(8) L. H. Slaugh and J. H. Raley, *Tetrahedron*, **20**, 1005 (1964).
(9) G. Soussar and P. Freon, *Compt. Rend., Ser. C*, **262**, 933 (1966).
(10) R. A. Carboni and R. V. Lindsay, Jr., *J. Am. Chem. Soc.*, **81**, 4342 (1959).

resonance 1,4-dianions as in **43** seems feasible.



41 **42** **43**

Although the present 1,4- and 1,6-dianions appear to be the first examples of such dianions that have been prepared from active hydrogen compounds by means of bases and employed in condensations, earlier workers[11] have prepared 1,4-dianion **45** from unsaturated hydrocarbon **44** by means of sodium or lithium in ether, as evidenced by carbonation to form the corresponding diacid in unreported yield.

44 **45**

The alkylation reactions described above furnish convenient methods of synthesis for many new compounds. These alkylation methods appear preferable in certain cases to the more common type of condensation of an appropriate ketone or aldehyde with phenylhydrazine or hydroxylamine. For example, the C-benzylation of phenylacetaldehyde phenylhydrazone (**3**) to form **9** (see Scheme II) is presumably more convenient than condensation of phenylhydrazine with 2,3-diphenylpropionaldehyde, which seems not readily available. Certainly, the C,N-dibenzylation of **3** to give **10** should be preferable to the condensation of 2,3-diphenylpropionaldehyde with N-benzylphenylhydrazine. Indeed, even some ketones or aldehydes might be prepared conveniently through the alkylation method, followed by hydrolysis. Thus, although diketone **30** may be made by the Friedel–Crafts acylation of benzene with suberic acid chloride, a corresponding *ortho*- or *meta*-substituted diketone might be obtained more conveniently from the appropriate oxime and 1,4-dibromobutane, followed by hydrolysis (see Scheme VIII). Similarly, while diketone **19** is readily obtained by the Friedel–Crafts condensation of succinyl chloride with benzene, certain *ortho*- or *meta*-substituted diketones might be prepared conveniently by the alkylation–hydrolysis process (see Scheme VII). Also, certain pyridazines of type **36** having *ortho* or *meta* substituents in the phenyl groups may be synthesized by the method indicated in Scheme X. Finally, the present method for the synthesis of pyridazine **39** appears more convenient than the earlier one involving tetrazine **40** (see Scheme XI).

Experimental Section[12]

Conversion of Acetophenone Phenylhydrazone (3) to Dipotassio Salt 4. To a stirred suspension of 0.05 mol of potassium amide in 300 ml of liquid ammonia,[13] prepared from 1.95 g (0.05 g-atom) of potassium,[14] was added, during 2 min, 5.25 g (0.025 mol) of acetophenone phenylhydrazone (**3**)[15] in 20 ml of anhydrous ether. After 1 hr, the resulting orange-brown suspension, which was assumed to contain 0.025 mol of dipotassio salt **4**, was employed as described below.

C-Alkylations of Dipotassio Salt 4. A. C-Benzylation with Benzyl Chloride to Form 5. To a stirred suspension of 0.0025 mol of dipotassio salt **4** was added, during 5 min, a solution of 3.15 g (0.025 mol) of benzyl chloride in 20 ml of anhydrous ether. After 1 hr, the tan reaction mixture was neutralized with excess solid ammonium chloride, and the ammonia was evaporated (steam bath). The residue was taken up into ether and water, and the ethereal layer was combined with two ethereal extracts of the aqueous layer. The ethereal solution was dried ($MgSO_4$) and concentrated to afford a yellow solid, which was indicated to contain one component by tlc. Recrystallization from methanol afforded 5.18 g (69%) of phenylhydrazone **5**, mp 77–79 and 79–80° after two recrystallizations from methanol; ir (KBr) 3340 (NH) and 1610 cm^{-1} (C=N, shoulder); nmr ($CDCl_3$) 128 (m, 4.1, CH_2CH_2) and 438 cps (m, 15.9 ArH plus NH). When the nmr sample was shaken with deuterium oxide, the peak at 438 cps integrated for 15.1 protons, indicating exchange of the NH proton.

Anal. Calcd for $C_{21}H_{20}N_2$: C, 83.96; H, 6.71; N, 9.33. Found: C, 83.61; H, 6.48; N, 8.86.

This compound decomposes on standing; this is the best of five analyses.

Independent synthesis of 5 was accomplished by refluxing a solution of 2.1 g (0.01 mol) of benzylacetophenone (**6**),[16] 1.1 g (0.01 mol) of phenylhydrazine, and 2 ml of glacial acetic acid in 30 ml of absolute ethanol for 1 hr. The yellow oil that separated on cooling the reaction mixture was removed and dissolved in hot methanol to precipitate, on cooling, 2.31 g (77%) of **5**, mp 77–80 and 79–80° after recrystallization from methanol. The mixture melting point with a sample of **5** obtained by alkalation of **4** was the same; the ir spectra of the two samples were identical.

B. Coupling with 2,3-Dibromo-2,3-dimethylbutane to Form Bisphenylhydrazone 18. To a stirred suspension of 0.025 mol of dipotassio salt **4** was added, during 15 min, 3.05 g (0.0125 mol) of 2,3-dibromo-2,3-dimethylbutane[5] in 50 ml of anhydrous ether to produce an immediate dark color which was slowly discharged to leave a light brown suspension. After 1 hr, excess ammonium chloride was added, and the reaction mixture was worked up as described above under A to give light tan crystals. Recrystallization from ethanol afforded 3.34 g (64%) of 1,4-diphenyl-1,4-butanedione diphenylhydrazone (**18**), mp 169–170° (white crystals); ir ($CHCl_3$) 3360 cm^{-1} (NH); nmr ($CDCl_3$) 136 (b, 4.0, CH_2CH_2), 388 (b, 1.8, NH), and 426 cps (m, 19.8, ArH).

Anal. Calcd for $C_{28}H_{26}N_4$: C, 80.36; H, 6.26; N, 13.39. Found: C, 80.61; H, 6.42; N, 13.20.

Independent synthesis of 18 was effected by refluxing a solution of 2.38 g (0.01 mol) of 1,4 diphenyl-1,4-butanedione (**19**),[17] 2.2 g (0.02 mol) of phenylhydrazine, and 2 ml of glacial acetic acid in 30 ml of absolute ethanol for 30 min. The light yellow solid that precipitated on cooling the reaction mixture was collected and recrystallized from ethanol to give 3.42 g (82%) of **18**, mp and mmp 168–170°; the ir spectra of the two samples were identical.

C. Twofold Alkylation with 1,4-Dibromobutane to Form Bisphenylhydrazone 20. To a stirred suspension of 0.025 mol of dipotassio salt **4** was added, during 5 min, 2.7 g (0.0125 mol) of 1,4-dibromobutane in 25 ml of anhydrous ether. After 1 hr, the light brown reaction mixture was neutralized with excess ammonium chloride and worked up as described above under A to give a dark brown tarry solid. This material was refluxed with ethanol, and the resulting mixture was filtered. The insoluble solid appeared to be polymeric material. The filtrate was concentrated and the re-

(11) W. Schlenk, *et al.*, *Ann.*, **463**, 98 (1928).

(12) Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on Perkin–Elmer spectrophotometers Models 137 and 237 using potassium bromide disks or chloroform solutions for solids and sodium chloride plates for liquids. The nmr spectra were obtained on a Varian A-60 spectrometer, in deuteriochloroform solution. All chemical shifts are reported in cycles per second (cps) downfield from an internal tetramethylsilane standard. In nmr descriptions s = singlet, t = triplet, d = doublet, m = multiplet, and b = broad. Vapor phase chromatography (vpc) was performed on an F & M Model 500 gas chromatograph using a 5-ft silicone gum column. Thin layer chromatography (tlc) was done with silica gel G (Merck). Analyses were performed by Paul Demoen, Janssen Pharmaceutical Research Laboratories, Beerse, Belgium, and M-H-W Laboratories, Garden City, Mich.

(13) Commercial anhydrous liquid ammonia was distilled and used immediately.

(14) See R. S. Yost and C. R. Hauser, *J. Am. Chem. Soc.*, **69**, 2325 (1947).

(15) This compound should be freshly prepared. See R. L. Shriner, W. C. Ashley, and E. Welch, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 725.

(16) This ketone was prepared by the reduction of chalcone: R. Adams, J. W. Kern, and R. L. Shriner, "Organic Syntheses," Coll. Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1941, p 101.

(17) See P. S. Bailey and R. E. Lutz, *J. Am. Chem. Soc.*, **70**, 2412 (1948).

sulting precipitate recrystallized to afford 1.46 g (24%) of 1,8-diphenyl-1,8-octanedione diphenylhydrazone (**20**), mp 128–130°; ir ($CHCl_3$) 3352 (NH) and 1622 cm^{-1} (C=N, shoulder); nmr ($CDCl_3$) 74 (m, 8.2, $(CH_2)_4$), 134 (m, 4.0, CH_2), 396 (b, 1.9, NH), and 436 cps (m, 19.6, ArH).

Anal. Calcd for $C_{32}H_{34}N_4$: C, 80.97; H, 7.22; N, 11.81. Found: C, 80.91; H, 7.31; N, 11.68.

When the reaction was repeated using 0.025 mol of dipotassio salt **4** and only 1.35 g (0.0063 mol) of 1,4-dibromobutane there was obtained 1.84 g (62%) of bisphenylhydrazone **20**, mp and mmp 127–130°, and only a little polymer. Most of the excess acetophenone phenylhydrazone was recovered.

Conversion of Phenylacetaldehyde Phenylhydrazone (7) to Dipotassio Salt 8. To a stirred suspension of 0.05 mol of potassium amide in 300 ml of liquid ammonia[13] was added 5.25 g (0.025 mol) of phenylacetaldehyde phenylhydrazone (**7**) in 20 ml of anhydrous ether. After 1 hr, the resulting dark red suspension, which was assumed to contain 0.025 mol of dipotassio salt **8**, was employed as described below.

C-Benzylation of Dipotassio Salt 8 to Form 9. A solution of 3.15 g (0.025 mol) of benzyl chloride in 20 ml of anhydrous ether was added, during 5 min, to a stirred suspension of dipotassio salt **8**. The dark red color of **8** was discharged locally as the halide was added; when all of the halide had been added, the color was orange tan. After 1 hr, the reaction mixture was neutralized with excess ammonium chloride and worked up as described for the benzylation of dipotassio salt **4** to give 4.58 g (61%) of phenylhydrazone **9**, mp 107–110°. Tlc indicated only one product. Recrystallization from methanol afforded **9**, mp 111–112°; ir (KBr) 3340 cm^{-1} (NH); nmr ($CDCl_3$) 146 (b, 1.9, CH_2), 205 (m, 1.0, CH), 3.62 (b, 1.0, NH), 431 (m, 15.1, ArH), and 572 cps (d, 1.0 aldehydic CH, J = 6.0 cps).

Anal. Calcd for $C_{21}H_{20}N_2$: C, 83.96; H, 6.71; N, 9.33. Found: C, 84.15; H, 6.82; N, 8.96.

C,N-Dibenzylation of Dipotassio Salt 8 to Form 10. A solution of 6.30 g (0.05 mol) of benzyl chloride in 20 ml of anhydrous ether was added, during 5 min, to a stirred suspension of 0.025 mol of dipotassio salt **8**. After 1 hr, the light brown reaction mixture was neutralized with excess ammonium chloride and worked up as described for the benzylation of dipotassio salt **4** to give a light brown solid. Recrystallization from methanol afforded 7.60 g (78%) of phenylhydrazone **10** (orange crystals), mp 103–105 and 104–105° after recrystallization from methanol; ir (no NH peak); nmr ($CDCl_3$) 140 (b, 1.9, CH_2), 212 (m, 1.0, CH), 285 (s, 2.0, NCH_2), 432 (m, 19.8, ArH), and 584 cps (d, 1.0, aldehydic CH, J = 6.0 cps).

Anal. Calcd for $C_{28}H_{26}N_2$: C, 86.11; H, 6.71; N, 7.17. Found: C, 86.32; H, 6.78; N, 6.97.

Other Preparations of Dibenzyl Derivative 10. A. By N-Benzylation of 9. To a stirred suspension of 0.01 mol of potassium amide in 300 ml of liquid ammonia[13] was added 3.0 g (0.01 mol) of phenylhydrazone **9** in 20 ml of anhydrous ether followed, after 30 min, by 1.26 g (0.01 mol) of benzyl chloride in 20 ml of anhydrous ether. After 1 hr, the light brown reaction mixture was neutralized with excess ammonium chloride and worked up to give, after recrystallization from methanol, 3.16 g (81%) of phenylhydrazone **10**, mp and mmp 104–105°. The infrared spectra of the two samples were identical.

B. By N-Benzylation of 7, Followed by C-Benzylation of 12. To a stirred suspension of 0.05 mol of potassium amide in 300 ml of liquid ammonia[13] was added 10.50 g (0.05 mol) of phenylacetaldehyde phenylhydrazone (**7**) in 20 ml of anhydrous ether to form monopotassio salt **11** (orange brown). After 30 min, 6.30 g (0.05 mol) of benzyl chloride in 20 ml of anhydrous ether was added during 5 min; the orange-brown color of **11** was discharged slowly (20–30 min). After 1 hr, the tan reaction mixture was neutralized and worked up to afford a light brown solid; tlc indicated only one component. Recrystallization from methanol afforded 9.6 g (64%) of phenylacetaldehyde N-benzylphenylhydrazone (**12**), mp 79.5–80°; ir (no NH peak); nmr ($CDCl_3$) 210 (d, 2.0, CH_2, J = 5.5 cps), 289 (s, 2.0, NCH_2), 424 (m, 14.9, ArH), and 576 cps (t, 1.0, aldehydic CH, J = 5.5 cps).

Anal. Calcd for $C_{21}H_{20}N_2$: C, 83.96; H, 6.71; N, 9.33. Found: C, 83.88; H, 6.83; N, 9.09.

C-Benzylation of 12 (0.025 mol) was effected by means of 0.025 mol each of potassium amide and benzyl chloride to give, after recrystallization from methanol, 6.73 g (69%) of **10**; mp, mmp 103–105°.

C,N-Dialkylation of Dipotassio Salt 8 with Two Different Halides. A. Benzylation Followed by Butylation. A solution of 3.15 g (0.025 mol) of benzyl chloride in 20 ml of anhydrous ether was added, during 5 min, to a stirred suspension of 0.05 mol of dipotassio salt **8** followed, after 30 min, by 3.43 g (0.025 mol) of *n*-butyl bromide in 20 ml of anhydrous ether. After 30 min, the reaction mixture was neutralized and worked up as described for the benzylation of dipotassio salt **4** to give a brown solid; tlc indicated one major component with small amounts of two other components. Recrystallization from ethanol afforded 5.17 g (58%) of phenylhydrazone **14** (light brown crystals), mp 123–125°; ir (no NH peak); nmr ($CDCl_3$) 82 (m, 9.4, $CH_2CH_2CH_2CH_3$), 200 (m, 0.9, CH), 282 (s, 2.0, NCH_2), 426 (m, 14.9, ArH), and 568 cps (d, 1.1 aldehydic CH, J = 6.0 cps).

Anal. Calcd for $C_{25}H_{28}N_2$: C, 84.22; H, 7.93; N, 7.86. Found: C, 84.01; H, 8.06; N, 7.99.

B. Butylation Followed by Benzylation. A solution of 3.43 g (0.025 mol) of *n*-butyl bromide in 20 ml of anhydrous ether was added to 0.05 mol of dipotassio salt **8** followed, after 30 min, by 3.15 g (0.025 mol) of benzyl chloride in 20 ml of anhydrous ether and the reaction mixture worked up as indicated under A. Recrystallization of the orange-brown solid from ethanol–benzene afforded 5.31 g (62%) of phenylhydrazone **13** (orange-brown crystals), mp 114–117°; ir (no NH peak); nmr ($CDCl_3$) 91 (m, 6.7, $CH_2CH_2CH_3$), 190 (m, 2.9, CH_2CH), 230 (m, 2.0, NCH_2), 433 (m, 15.4, ArH), and 588 cps (d, 1.0, aldehydic CH, J = 6.0 cps).

Anal. Calcd for $C_{25}H_{28}N_2$: C, 84.22; H, 7.93; N, 7.86. Found: C, 84.01; H, 7.99; N, 8.08.

C,N-Dialkylation of Deoxybenzoin Phenylhydrazone (15) to Form 16. Phenylhydrazone **15** (0.025 mol) was converted to its dipotassio salt with 0.05 mol of potassium amide in liquid ammonia,[13] and, after 1 hr, this salt was treated with 0.025 mol of *n*-butyl bromide in ether followed, after 30 min, by 0.025 mol of benzyl chloride in ether essentially as indicated above for the C,N-dialkylation to phenylacetaldehyde phenylhydrazone. The reaction mixture was neutralized and worked up to afford, after recrystallization of the product from benzene–acetonitrile, 5.84 g (54%) of the C,N-dialkyl derivative **16**, mp 172–173°; ir (no NH peak); nmr ($CDCl_3$) 75 (m, 8.9, C_4H_9), 190 (m, 1.0, CH), 290 (s, 2.0, NCH_2), and 443 cps (m, 17.9, ArH).

Anal. Calcd for $C_{31}H_{32}N_2$: C, 86.07; H, 7.46; N, 6.48. Found: C, 85.89; H, 7.54; N, 6.46.

C-Benzylation of Deoxybenzoin Oxime (21) through Its Dipotassio Salt 22 to Form 23. To a stirred suspension of 0.05 mol of potassium amide in 300 ml of liquid ammonia[13,14] was added, during 2 min, 5.28 g (0.025 mol) of deoxybenzoin oxime (**21**) in 20 ml of anhydrous ether to form a bright red suspension of dipotassio salt **22**. After 1 hr, 3.15 g (0.025 mol) of benzyl chloride in 20 ml of anhydrous ether was added to discharge the color of **22**. After 1 hr, the yellow reaction mixture was neutralized with ammonium chloride and processed as described above for the C-benzylation of dipotassio phenylhydrazone **4** to give, after recrystallization from ethanol, 3.46 g (46%) of 2,3-diphenylpropiophenone oxime **23**, mp 176–182 and 182–184° after two more recrystallizations; ir ($CHCl_3$) 3410 cm^{-1} (OH, broad); nmr ($CDCl_3$) 151 (m, 2.0, CH_2), 223 (m, 0.9, CH), 382 (b, 0.9, OH), and 420 cps (m, 14.8, ArH).

Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.51; H, 6.47; N, 4.73.

Independent synthesis of 23 was effected by refluxing a mixture of 2.86 g (0.01 mol) of ketone **24**,[18] 1.36 g (0.02 mol) of hydroxylamine hydrochloride, 20 ml of 10% potassium hydroxide solution, and 30 ml of ethanol for 1 hr. Upon cooling, a white solid precipitated. Filtration yielded white crystals which were recrystallized from ethanol to give 2.16 g (72%) of oxime **23**, mp 180–183°, mmp 179–182°; the ir spectra of the two samples were identical.

Attempted C-Benzylation of Acetophenone Oxime (25) by Means of Potassium Amide. This experiment was performed as described above for the C-benzylation of deoxybenzoin oxime (**21**). A purple color was produced. There was obtained mainly stilbene[7] (from benzyl chloride) and recovered acetophenone (from acetophenone oxime), which were identified by vpc.

Conversion of Acetophenone Oxime (25) to Dilithio Salt 26. A solution of 3.38 g (0.025 mol) of acetophenone oxime (**25**) in 25 ml of tetrahydrofuran[19] (THF) was added under nitrogen, during 5

(18) This ketone was prepared by a base-catalyzed condensation of deoxybenzoin with formaldehyde followed by conjugate addition of the resulting α,β-unsaturated ketone with phenylmagnesium bromide: H. Fiesselmann and J. Ribca, *Chem. Ber.*, **89**, 27 (1956).

(19) Freshly distilled from lithium aluminum hydride.

min, to a mixture of 32 ml (0.05 mol) of 1.6 *M* *n*-butyllithium in hexane[20] and 200 ml of THF[19] at −80°. After 1 hr, the clear orange-yellow solution, which was assumed to contain 0.025 mol of dilithio salt **26**, was employed as described below.

C-Alkylation of Dilithio Salt 26. A. With Benzyl Chloride to Form 27. A solution of 3.15 g (0.025 mol) of benzyl chloride in 20 ml of THF[19] was added to a stirred solution of 0.025 mol of dilithio salt **26** at −80°. After 30 min, the yellow reaction mixture was warmed to room temperature during 1 hr, and 100 ml of water then added. After stirring, the layers were separated. The organic layer was combined with two ethereal extracts of the aqueous layer, and the solution was dried ($MgSO_4$) and concentrated. The resulting white solid was recrystallized from methanol giving 4.17 g (74%) of benzylacetophenone oxime (**27**), mp 86–87° (lit.[21] mp 87°).

Independent synthesis of 27 (mp and mmp 86–87°) was effected in 82% yield by condensation of benzylacetophenone[16] (**6**) with hydroxylamine essentially as described above for the independent synthesis of oxime **23**; the ir spectra of the two samples of **27** were identical.

B. Coupling by 2,3-Dibromo-2,3-dimethylbutane to Form Bisoxime 28. To a stirred solution of 0.025 mol of dilithio salt **26** was added, during 15 min, 3.05 g (0.0125 mol) in 50 ml of THF to produce an orange suspension, which slowly dissolved to an orange solution. After 1 hr, 100 ml of water was added, and the reaction mixture was worked up as described above under A. The resulting white solid was recrystallized from ethanol to give 3.89 g (58%) of 1,4-diphenyl-1,4-butanedione dioxime (**28**), mp 207–208° (lit.[8] mp 209°); ir ($CHCl_3$) 3420 cm^{-1} (OH, broad).

Independent synthesis of 28 (mp and mmp 206–208°) was effected in 62% yield by condensation of 1,4-diphenyl-1,4-butanedione (**19**) with hydroxylamine essentially as described above for the independent synthesis of oxime **23**; the ir spectra of the two samples are identical.

C. Twofold Alkylation with 1,4-Dibromobutane to Form Bisoxime 29. To a stirred solution of 0.025 mol of dilithio salt **26** was added, during 5 min, 2.7 g (0.0125 mol) of 1,4-dibromobutane in 25 ml of THF.[19] After 1 hr, the yellow reaction mixture was neutralized with 100 ml of water and worked up as described above under A. The yellow product was refluxed with ethanol and the mixture filtered. The insoluble solid appear to be polymeric material. The filtrate was concentrated and the resulting precipitate recrystallized from ethanol to give 2.67 g (32%) of 1,8-diphenyl-1,8-octanedione dioxime (**29**), mp 192–193° (lit.[9] mp 193°); ir ($CHCl_3$) 3380 cm^{-1} (OH, broad).

When the reaction was repeated using 0.025 mol of dilithio salt **26** and only 0.0063 mol of 1,4-dibromobutane, there was obtained 1.42 g (42%) of recovered acetophenone oxime (**25**), mp and mmp 58–59° (recrystallized from methanol), and 2.70 g (66%) of **29**, mp and mmp 192–193° (recrystallized from ethanol). Only a little polymeric material was produced.

Hydrolysis of bisoxime 29 was effected by refluxing a solution of 3.24 g (0.01 mol) of it with 20 ml of 20% hydrochloric acid for 2 hr. The mixture was cooled to precipitate a white solid, which was collected and recrystallized from ethanol to give 2.18 g (74%) of 1,8-diphenyl-1,8-octanedione (**30**), mp 86° (lit.[9] mp 85°); ir ($CHCl_3$) 1680 cm^{-1} (C=O).

Conversion of Acetophenone Azine (31) to Its Dilithio Salt 32. A solution of 5.9 g (0.025 mol) of acetophenone azine (**31**) in 25 ml of anhydrous ether was added under nitrogen, during 5 min, to a mixture of 32 ml (0.05 mol) of 1.6 *M* *n*-butyllithium in hexane[20] and 200 ml of anhydrous ether at 0°. After 1 hr, the orange-brown suspension which was assumed to contain 0.025 mol of dilithio salt **32** was employed as described below.

C-Dibenzylation of Dilithio Salt 32 to Form 33. A solution of 6.30 g (0.05 mol) of benzyl chloride in 30 ml of anhydrous ether was added, during 5 min, to a stirred suspension of 0.025 mol of dilithio salt **32** at 0°; after warming to room temperature during 1 hr, the reaction mixture was acidified with 100 ml of 3 *N* hydrochloric acid, and the layers were separated. After being washed with ether, the aqueous acidic layer was neutralized with sodium carbonate, and the resulting mixture was extracted with ether. The ethereal extract was dried ($MgSO_4$) and the solvent removed. The yellow solid residue was recrystallized from methanol–acetonitrile to give 5.88 g (56%) of benzylacetophenone azine (**33**, yellow crystals), mp 111–112°; the ir spectrum was like that of the starting azine **31**; nmr ($CDCl_3$) 180 (m, 8.0, CH_2CH_2) and 439 cps (m, 20.0, ArH).

Anal. Calcd for $C_{30}H_{28}N_2$: C, 86.50; H, 6.78; N, 6.73. Found: C, 86.29; H, 6.78; N, 6.78.

Independent synthesis of azine 33 was affected by refluxing 4.20 g (0.02 mol) of benzylacetophenone[16] (**6**) with 0.32 g (0.01 mol) of hydrazine in 30 ml of absolute ethanol for 1 hr. The yellow solid that precipitated on cooling was collected and recrystallized from methanol–acetonitrile to give 2.99 g (72%) of azine **33**, mp and mmp 111–112°.

C-Dibenzylation of Azine 31 to Form 33 and Stilbene with Potassium Amide. Treatment of 0.05 mol of potassium amide in liquid ammonia with 0.025 mol of acetophenone azine (**31**) in ether followed, after 1 hr, by 0.05 mol of benzyl chloride in ether produced a purple color to afford stilbene and recovered starting azine **31.**

When the experiment was repeated and the liquid ammonia replaced under nitrogen with THF[19] before adding the halide, there was obtained, along with stilbene, 6.33 g (32%) of dibenzyl derivative **33**, mp and mmp 111–112°.

Cyclization of Dilithio Salt 32 by 2,3-Dibromo-2,3-dimethylbutane to Form Dihydropyridazine 35. To a stirred suspension of 0.025 mol of dilithio salt **32** was added, during 15 min, 6.10 g (0.025 mol) of 2,3-dibromo-2,3-dimethylbutane[5] in 50 ml of anhydrous ether. After 1 hr, the reaction was acidified and worked up as described for the C-dibenzylation of dilithio salt **32** to give, after several recrystallizations from ethanol–benzene, 2.22 g (40%) of 3,6-diphenyl-4,5-dihydropyridazine (**35**), mp 143–146° (lit.[22] mp 149); the ir spectrum was like that of the starting azine **31**; the compound was too insoluble for an nmr determination.

Anal. Calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 81.84; H, 6.21; N, 11.79.

Also, tlc on the crude product had indicated the presence of some 3,6-diphenylpyridazine (**36**).

Oxidation of the crude product was effected with an alkaline solution of hydrogen peroxide in hot ethanol[22] to give, after recrystallization from acetic acid, 4.71 g (81% from azine **31**) of 3,6-diphenylpyridazine (**36**), mp 221° (lit.[22] mp 222°).

Independent syntheses of dihydropyridazine (**35**) and of 3,6-diphenylpyridazine (**36**) were effected by refluxing 2.38 g (0.01 mol) of 1,4-diphenyl-1,4-butanedione (**19**) with 0.32 g (0.01 mol) of hydrazine in 20 ml of absolute ethanol for 2 hr. The brown solid that precipitated on cooling was collected and recrystallized several times from ethanol–benzene to give a small amount of pure dihydropyridazine **35**, mp and mmp 143–146°. Tlc on the crude product had indicated the presence of diazine **36**. The experiment was repeated and the crude product was oxidized with alkaline hydrogen peroxide to give diazine **36** in 74% over-all yield. A mixture melting point with a sample of **36** obtained from **31** was the same; also the ir spectra of the two samples were identical.

Preparation of Azine 37. A solution of 13.4 g (0.10 mol) of acetophenone hydrazone,[23] 19.6 g (0.10 mol) of deoxybenzoin, and 2 ml of glacial acetic acid in absolute ethanol was refluxed for 6 hr. The yellow solid that precipitated on cooling was recrystallized from hexane–benzene to give 20.03 g (64%) of azine **37**, mp 156–157°; ir ($CHCl_3$) 1614 cm^{-1} (C=N, shoulder); nmr ($CDCl_3$) 118 (s, 3.0, CH_3), 214 (s, 2.0, CH_2), and 436 cps (m, 14.8, ArH).

Anal. Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.46; H, 6.32; N, 9.31.

Conversion of Azine 37 through Dihydropyridazine 38 to Pyridazine 39. A solution of 7.95 g (0.025 mol) of azine **37** in 25 ml of anhydrous ether was added to a stirred solution of 32 ml (0.05 mol) of 1.6 *M* *n*-butyllithium[20] in ether–hexane followed, after 1 hr, by 6.10 g (0.025 mol) of 2,3-dibromo-2,3-dimethylbutane,[5] and the reaction mixture worked up as described above for the cyclization of azine salt **32**. The crude brown product, which was indicated by tlc to consist of two components, was heated with a mixture of 2 g of sodium hydroxide, 10 ml of 30% hydrogen peroxide, and 50 ml of ethanol on the steam bath for 1 hr. The solid that precipitated on cooling was recrystallized from ethanol to afford 6.01 g (78%) of 3,4,6-triphenylpyridazine (**39**), mp 171–172° (lit.[10] mp 176–177.5° (corr)); uv max (95% ethanol) 272 mμ (ε max 28,000).

Anal. Calcd for $C_{22}H_{16}N_2$: C, 85.69; H, 5.23; N, 9.09. Found: C, 85.38; H, 5.29; N, 9.14.

(20) Obtained from the Foote Mineral Co., Exton Pa.

(21) W. Schneidewind, *Ber.*, 21, 1323 (1888).

(22) K. Alder, H. Niklas, R. Aumuller, and B. Olson, *Ann.*, **585**, 81 (1954).

(23) G. P. Newkome and D. C. Fishel, *J. Org. Chem.*, **31**, 677 (1966).