Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 78.42; H, 7.55; N, 8.45.

5,7-Diphenyl-1,3-diazaadamantan-6-one *N*-Oxide (4).—A mixture of **1a** (300 mg, 0.987 mmol) and *m*-chloroperbenzoic acid (520 mg, 3.00 mmol) in chloroform (20 ml) was refluxed for 13 hr. After cooling, excess peracid was decomposed by adding 10% aqueous sodium bisulfite solution and the mixture was extracted with 10% aqueous sodium carbonate solution (3 × 10 ml). The organic layer was dried (Na_2SO_4) and the solvent was removed to afford a crude product which was purified on a silica gel column eluting with a $CHCl_3$–EtOH system to give **4** as colorless crystals (100 mg, 32%): mp 258–261°; mass spectrum *m/e* (rel intensity) 320 (12, M^+), 304 (72), 261 (100), 260 (57), 247 (24), 233 (24), 159 (19), 144 (23), 131 (32), and 103 (46). Treatment of **4** with trifluoroacetic acid gave quantitatively trifluoroacetate salt **5**: mp 177–181°; ir (KBr) 1725 (CO), 1670 (COO^-), and 1190 cm^{-1} (CF_3).

Anal. Calcd for $C_{22}H_{21}N_2O_4F_3$: C, 52.76; H, 3.69; N, 5.12. Found: C, 52.81; H, 3.93; N, 5.12.

***N,N'*-Diformylbispidin-9-one (6a).**—To a vigorously stirred mixture of **1a** (300 mg, 0.987 mmol), triethylbenzylammonium chloride (20 mg, 0.088 mmol), benzene (5 ml), and 50% sodium hydroxide aqueous solution (10 ml) was added dropwise a mixture of benzene (5 ml) and chloroform (0.80 ml, 9.9 mmol) at 25° in *ca.* 0.5 hr. After the addition was completed, the stirring was continued for a further 22 hr, and the mixture was diluted with water (60 ml) and extracted with chloroform (2 × 30 ml). The combined extracts were dried (Na_2SO_4) and evaporated to give a crude product, which was chromatographed on a silica gel column ($CHCl_3$–EtOH) to afford **6a** as colorless crystals (80 mg, 23%): mp 229–232°; ir (KBr) 1720 (CO) and 1680 cm^{-1} (NCHO); nmr ($CDCl_3$) τ 1.98 (s, 2, 2 CHO), 2.69 (s, 10, 2 C_6H_5), 4.80 (d of d, 2, J = 13 and 2 Hz, C_2H_{eq} anti to oxygen atom of the formyl carbonyl), 5.95 (AB q, 4, J = 13 Hz, $J/\Delta\tau$ = 0.542, 2 CH_2 at C_4 and C_8 syn to oxygen atom of the formyl carbonyl), and 6.55 (d of d, 2, J = 13 and 2 Hz, C_2H_{ax} and C_6H_{ax} anti to the formyl carbonyl);[22] mass spectrum *m/e* (rel intensity) 348 (100, M^+), 320 (36), 277 (73), 276 (95), 248 (32), 233 (26), 207 (34), 205 (32), 105 (62), 103 (51), 97 (41), 85 (41), 83 (45), 71 (57), 69 (47), 57 (95), 44 (53), 43 (85), 41 (42), and 40 (38).

Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.39; H, 5.79; N, 8.04. Found: C, 72.40; H, 6.04; N, 7.88.

5,7-Diphenyl-1,3-diazaadamantan-6-one Hydrazone (7).—A mixture of **1a** (600 mg, 1.97 mmol) and 80% hydrazine hydrate (5.00 g, 80.0 mmol) in diethylene glycol (20 ml) was refluxed with a Dean–Stark trap for 18 hr. The cooled mixture was diluted with water (50 ml) and extracted with chloroform (20 ml). The extract was washed with water (2 × 10 ml) and dried (Na_2SO_4). Removal of the solvent and chromatography of the crude product on a silica gel column ($CHCl_3$–EtOH) afforded **7** as colorless crystals (390 mg, 62%): mp 249–251°; mass spectrum *m/e* (rel intensity) 318 (19, M^+), 275 (32), 247 (14), 223 (15), 205 (14), 175 (13), 150 (34), 141 (15), 119 (13), 105 (13), 104 (20), 97 (14), 95 (12), 93 (13), 91 (14), 85 (17), 83 (17), 81 (14), 76 (20), 71 (30), 69 (26), 57 (70), 56 (40), 55 (34), 44 (32), 43 (32), 41 (62), and 40 (100); ir (KBr) 3425 and 3305 cm^{-1}; nmr ($CDCl_3$) τ 2.65 (s, 5, C_6H_5), 2.83 (s, 5, C_6H_5), 5.70 (s, 2, disappeared on deuteration, NH_2), 5.89 (s, NCH_2N), 6.15 (d of d, 4, J = 12 and 4 Hz, C_4H_{ax}, C_8H_{ax}, C_9H_{ax}, and $C_{10}H_{ax}$), and 6.53 (d of d, 4, J = 12 and 3 Hz, C_4H_{eq}, C_8H_{eq}, C_9H_{eq}, and $C_{10}H_{eq}$).

Anal. Calcd for $C_{20}H_{22}N_4$: C, 75.44; H, 6.96; N, 17.60. Found: C, 75.21; H, 6.96; N, 17.82.

Reaction of 1a with Tosylhydrazide.—A mixture of **1a** (160 mg, 0.83 mmol), tosylhydrazide (200 mg, 1.08 mmol), and barium oxide (2.0 g, 13.1 mmol) in ethanol was heated at 65° with occasional stirring for 3 days. After removal of the solids by filtration, the filtrate was evaporated to dryness to give crude product, which on purification by preparative tlc (silica gel, 5% MeOH–$CHCl_3$) afforded recovered **1a** (110 mg, 80% recovery) and 5,7-diphenyl-1,3-diazaadamantan-6-ol (**8**) (30 mg, 20%), mp 282–284° (lit.[7a] mp 274°), identified by spectral (ir and nmr) comparison with an authentic sample.[7a]

Treatment of 7 with Potassium *tert*-Butoxide in Dimethyl Sulfoxide.—To a solution of potassium *tert*-butoxide (40 mg, 0.36 mmol) in freshly distilled (from KOH) dimethyl sulfoxide (4 ml) was added **7** (60 mg, 0.19 mmol) and the resulting solution was stirred for 22 hr at room temperature under nitrogen atmosphere. The mixture was poured onto ice–water (30 ml) and extracted with methylene chloride (4 × 20 ml). The combined extracts were dried (Na_2SO_4) and evaporated to afford **8** (47 mg, 80%).

pK_a' Measurements.—pK_a' measurements were carried out by titrating potentiometrically an acidic solution of each amine (prepared by dissolving *ca.* 2.5 mg of amine into 3.00 ml of 0.01 *N* hydrochloric acid) with 0.1 *N* potassium hydroxide aqueous solution at 19°. The titration was performed on a Radiometer Model TT1.

Registry No.—**1a**, 19066-35-4; **1b**, 38740-11-3; **2a**, 38740-12-4; **2b**, 38740-13-5; **3**, 38740-14-6; **4**, 38740-15-7; **5**, 38740-16-8; **6a**, 38740-17-9; **7**, 38740-18-0; **8**, 3576-75-8; ammonium acetate, 631-61-8; dimethyl acetonedicarboxylate, 1830-54-2; dibenzyl ketone, 1083-30-3; ethylenediammonium acetate, 38734-69-9; trifluoroacetic acid, 76-05-1; tosylhydrazide, 1576-35-8.

(22) The formyl group seems to rotate not freely at room temperature, and hence two formyl groups in **6a** take preferably the anti conformation to each other by dipole–dipole interaction, though further details on this problem will be published elsewhere: *cf.* ref 6 and references cited therein.

Azodicarboxylic Acid Esters as Dealkylating Agents[1]

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The use of azodicarboxylic acid esters as dealkylating agents has been studied. The isolation and structure proof of the intermediate adducts obtained from the reaction of the azo esters with secondary and tertiary amines is reported. Dealkylation of compounds other than amines by this method is also discussed.

The diesters of azodicarboxylic acid (**1**, **2**) react with aliphatic primary amines to give amides,[2–4] while primary aromatic amines yield either triazan addition compounds[4–6] or ring-substituted systems.[6,7] It was reported that whereas piperidine reacts with diethyl azodicarboxylate (**1**) to yield the corresponding azodicarboxamide, other secondary amines combined with one molecule of this ester to give a stable addition product.[3,4] On acidic hydrolysis these adducts produced aldehydes in relatively low yields. Diels[3] assigned structure **3** to these adducts and later Kenner and Stedman,[8] utilizing infrared evidence, proposed the triazan structure **4**.

Diels was the first to investigate the reaction of the

(1) Taken in part from the dissertation presented by A. Makriyannis, March 1967, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy degree.

(2) O. Diels, *Justus Liebigs Ann. Chem.*, **429**, 1 (1922).

(3) O. Diels and M. Paquin, *Chem. Ber.*, **46**, 2000 (1913).

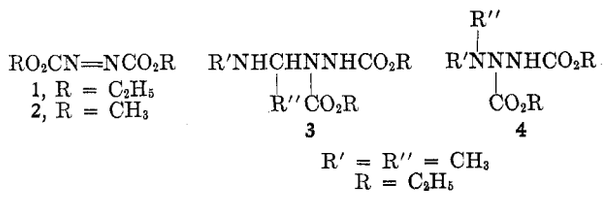
(4) O. Diels and P. Fritzsche, *ibid.*, **44**, 3018 (1911).

(5) K. E. Cooper and E. H. Ingold, *J. Chem. Soc.*, 1894 (1926).

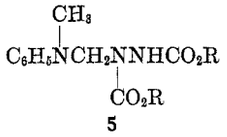
(6) G. S. Misra and S. B. Srivastava, *J. Indian Chem. Soc.*, **37**, 177 (1960).

(7) O. Diels, *Chem. Ber.*, **54**, 213 (1921).

(8) G. W. Kenner and R. J. Stedman, *J. Chem. Soc.*, 2089 (1952).

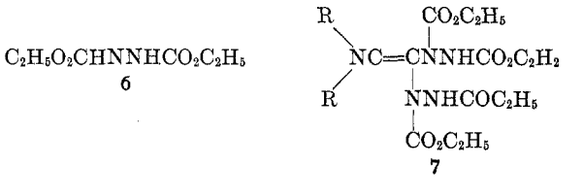


azodicarboxylic acid esters with tertiary alkylamines.[3,4] When *N*,*N*-dimethylaniline was used, a compound corresponding to the addition of one molecule of amine to one molecule of the azo ester was obtained. On acidic hydrolysis he obtained the corresponding monodemethylated amine and formaldehyde. He favored structure **5** as representing the adduct. Kenner



and Stedman[8] provided evidence to substantiate this proposed structure and suggested that its formation involved initial coordination of the basic nitrogen atom with the electrophilic azo group followed by a two-step ylide rearrangement. Huisgen and Jakob[9] provided some evidence in support of a similar mechanism.

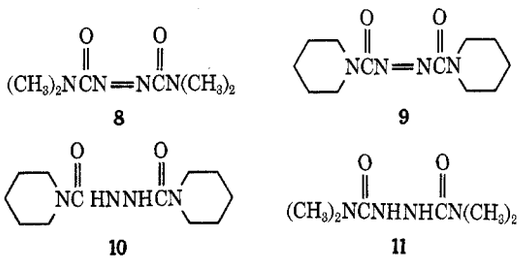
Tertiary amines containing the CHCHN– grouping were recently reported[10] to react with **1** in two steps through a different mechanism. In the first step a dehydrogenation takes place leading to diethyl hydrazodicarboxylate (**6**) and the corresponding enamines. The enamines can then react further with **1**, yielding the corresponding mono- or diadducts (**7**) which can



hydrolyze readily in acidic media to the secondary amines.

In these laboratories an investigation of the use of azodicarboxylic acid esters as dealkylating agents led to the isolation and conclusive structure proof of the adducts obtained from the reaction of the azo ester with secondary or tertiary amines. The investigation also provided information for the determination of the relative ease of dealkylation of unsymmetrically substituted tertiary aliphatic amines. A further study as to the possibility of using azo esters to dealkylate ethers and thio ethers was also performed.

Reaction with Secondary Amines.—When either **1** or **2** was allowed to react with a solution of dimethylamine or piperidine in ether, the reaction occurred at the ester carbonyl carbon of the azo ester, giving rise to *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (**8**) and azodicarboxyldipiperidide (**9**), respectively. When dimethylamine was mixed with **2** in a methanol–ether (1:1) or an ethanol–ether (1:1) solution, **8** was the only product isolated. However, when **1** was used under similar conditions the diamide **8** was only a minor product. The major product resulted from reaction at the azo nitrogen. This colorless addition product was characterized from its infrared and nmr spectra as diethyl 1,1-dimethyltriazane-2,3-dicarboxylate (**4**), the structure suggested by Kenner and Stedman. Piperidine yielded only the diamide **9** with both esters.



Following the failure to obtain the piperidyl adduct of the azo ester, the piperidyl adduct of **9** was sought. Reaction of **9**, however, with excess piperidine either by refluxing or by allowing the mixture to stand at room temperature for 1 week afforded a crystalline product identified as hydrazodicarboxyldipiperidide (**10**).

The difference in reactivity between **1** and **2** can be attributed to the larger steric effects operating at the carbonyl reaction center in the case of **1**. Piperidine, on the other hand, owing to its considerable bulk, was incapable of reacting with the azo nitrogen even under severe conditions.

The nmr spectrum of **8** in deuteriochloroform consisted of two sharp singlets at δ 3.00 and 3.12 ($\Delta\delta_{AB}$ 0.12) each due to six protons. Furthermore the nmr spectrum of **9** in carbon tetrachloride showed the presence of two equivalent, partially overlapping broad peaks at δ 3.15–3.77 ($\Delta\delta_{AB}$ 0.27) due to the methylene groups α to the amido nitrogen. When the solvent was changed to benzene a strong general upfield shift of the peaks was observed. The magnitude of this upfield shift was distinctly larger with the singlet situated higher upfield ($\Delta\delta_{AB}$ 0.20) in the case of **8** as well as with the broad peak situated higher upfield ($\Delta\delta_{AB}$ 0.31) in the case of **9**.

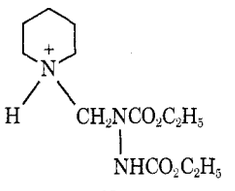
The observations mentioned above constitute evidence for the nonequivalence of the amide alkyl groups and indicate some conformational rigidity in the system. Similar observations concerning the nonequivalence of the two methyl groups in *N*,*N*-dimethylamides have been reported.[11,12]

Examination of the nmr spectrum of **10** in deuteriochloroform revealed that there was only one broad peak (δ 3.24–3.62) due to the four methylene protons α to the amido nitrogen. This observation, in conjunction with the absence of any significant solvent effect, provides evidence for a lack of conformational rigidity in this system.

Reaction with Tertiary Amines.—When *N*-methylpiperidine was allowed to react with **2**, a white, crystalline compound was isolated from the reaction mixture. The elemental analysis of the compound was compatible with a structure obtained from the addition of one

(9) R. Huisgen and F. Jakob, *Justus Liebigs Ann. Chem.*, **590**, 37 (1954).
(10) M. Colonna and L. Marchetti, *Gazz. Chim. Ital.*, **99**, 14 (1969).
(11) J. V. Hatton and R. E. Richards, *Mol. Phys.*, **5**, 153 (1962).
(12) L. A. LaPlanche and M. T. Rogers, *J. Amer. Chem. Soc.*, **86**, 337 (1964).

molecule of the amine to one of the azo ester. Acid hydrolysis of the compounds afforded equimolar amounts of formaldehyde, piperidine, and dimethyl hydrazodicarboxylate. The infrared spectrum of the compound showed absorptions at 3350, 1740, and 1750 cm^{-1}, indicating the presence of an NH group and two nonequivalent carbonyl groups. The nmr spectrum furnished conclusive evidence that the isolated adduct was diethyl *N*-(piperidinomethyl)-hydrazine-*N*,*N*′-dicarboxylate. The product obtained from the reaction between **1** and *N*-methylpiperidine, when isolated as its hydrochloride salt, was identified by infrared and nmr analysis as diethyl *N*-(piperidinomethyl)hydrazine-*N*,*N*′-dicarboxylate hydrochloride (**12**).



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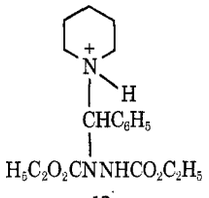

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N-Benzylpiperidine, when allowed to react with **1**, afforded an adduct whose hydrochloride salt was identified as diethyl *N*-(piperidinobenzyl)hydrazine-*N*,*N*′-dicarboxylate hydrochloride (**13**). This compound was extremely hygroscopic and labile, hydrolyzing spontaneously into equimolar amounts of benzaldehyde, piperidine, and **6**.

The relative ease of dealkylation of the different alkyl groups was determined by performing the reaction on a number of unsymmetrically substituted tertiary amines (Table I).

TABLE I
DEALKYLATION OF TERTIARY AMINES USING DIETHYL AZODICARBOXYLATE[a]

Amine	Dealkylation, % CH_3	C_2H_5 or C_3H_5	$C_6H_5CH_2$
N,*N*-Diethylmethylamine	14	83	
N-Methylpiperidine	73		
N-Ethylpiperidine		83	
N-Benzylpiperidine			91
N,*N*-Dimethylbenzylamine[b]	11		89
N,*N*-Diethylbenzylamine		67	33
N,*N*-Di-*n*-propylbenzylamine		56	38
N,*N*-Diisopropylbenzylamine		48	52

[a] It was found that there was no significant difference in these results when **2** was used instead of **1**. [b] The results of the dealkylation of *N*,*N*-dimethylbenzylamine shown here differ sharply from those reported by Kenner and Stedman.[8] Those investigators using dibenzyl azodicarboxylate reported only the adduct resulting from the reaction of a methyl group of the tertiary amine.

The effect of ring substitution on the reactivity of the benzyl group was studied by allowing a number of ring-substituted *N*,*N*′-diethylbenzylamines to react with **1** (Table II).

In every case the reaction mixture was analyzed by gas–liquid chromatography to determine the amounts of the different secondary amines obtained from the dealkylation of the corresponding tertiary amine.

TABLE II
DEALKYLATION OF SUBSTITUTED *N*,*N*-DIETHYLBENZYLAMINES USING DIETHYL AZODICARBOXYLATE

Substituent	Debenzylation, %
p-H	33
p-OCH_3	55
p-CH_3	39
p-Cl	40
p-NO_2	96

In the case of disubstituted benzylamines the amount of debenzylation could also be determined by measuring the amount of benzaldehyde obtained.

The method of analysis was based on the observation that when an aqueous solution of the tertiary amine–azo ester hydrochloride salt adduct was injected into a gas chromatograph having a hot injection port (220–240°), spontaneous hydrolysis of the adducts occurred. This method of analysis proved satisfactory when tested on standards.

The overall rate of the reaction between the azo esters and the tertiary amines[13] appeared to be greatly affected by the nucleophilicity of the latter. The reactivity of *N*,*N*′-dialkylbenzylamines decreased with an increase in the bulk of the alkyl substituents in the following order: isopropyl < *n*-propyl < Et < Me. The same was observed with the substituted piperidines, where benzyl < Et, Me. The para-substituted *N*,*N*′-diethylbenzylamines reacted in the order OCH_3 > CH_3, H > Cl > NO_2, the more basic amines reacting faster.

The reaction of the tertiary amine alkyl groups with azodicarboxylate esters proceeds by two different mechanisms depending on the presence or absence of alkyl hydrogens β to the amino nitrogen. They appear to have a common first step: the nucleophilic attack of the amino nitrogen on the azo group.

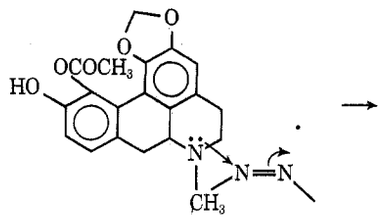
Preferential demethylation occurred only in the case of *N*-methylpiperidine, where ring dehydrogenation is less favored, probably because of stereoelectric considerations.[10]

The comparison of the reactivity of the benzylic position in para-substituted *N*,*N*-diethylbenzylamines does not present a clear picture of the electronic factors involved in this reaction. However, the fact that the *p*-nitro compound possesses by far the most reactive benzylic position is compatible with the suggested ylide intermediate.[8,9]

When *O*-acetyl bulbocapnine (**14**) was allowed to react with **1**, a pale, crystalline compound insoluble in dilute acid and alkali was obtained. When the compound was subjected to hydrolysis with dilute sulfuric acid, only the *O*-acetyl group was cleaved to give the free phenol while the remainder of the molecule remained intact. Based on further infrared and nmr evidence the product of this reaction, which probably proceeded through the mechanism outlined below, was identified as 1-[2-[(*N*,*N*′-dicarbethoxyhydrazino)-methylamine]ethyl]-3,4-methylenedioxy-5-acetoxy-6-methoxyphenanthrene (**15**).

Reaction with Ethers and Thioethers.—A study of the dealkylation of ethers and thioethers was initiated. The reactions of **1** with dibenzyl ether and dibenzyl

(13) The relative reactivities of the tertiary amines were based on their observed reaction times with the azo esters.



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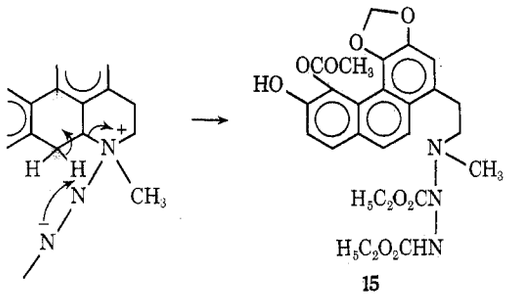

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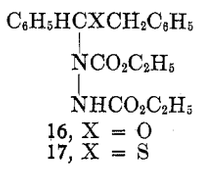
thioether were performed in the absence of solvent. It was found that heating to 100° was sufficient to initiate the reaction, no ultraviolet irradiation being necessary.[14,15] The free radicals appear to originate from the thermal decomposition of the azo ester. Both adducts obtained (**17**, **18**) were labile in the presence of moisture.



16, X = O
17, X = S

The method of analysis of the products was based on the observation that when an acidic solution of the adduct was injected into a gas chromatograph having a hot injection port (220–240°), complete spontaneous hydrolysis occurred. Determination of the benzaldehyde obtained from these reaction mixtures indicated that the dealkylations occurred quantitatively.

Experimental Section[16]

***N,N,N′,N′*-Tetramethylazodicarboxamide** (**8**).—To a cooled solution of diethyl azodicarboxylate (**1**, 1.00 g, 5.74 mmol) in 20 ml of anhydrous Et_2O, Me_2NH (0.50 g, 11.09 mmol) was added slowly with continuous stirring. The mixture was allowed to stand at 0° for 2 hr and the yellow flakes which formed were filtered and washed with a small amount of anhydrous Et_2O. The filtrate was concentrated to a volume of 10 ml and allowed to stand at 0° for 12 hr. A second crop of crystals was filtered and washed with a small amount of anhydrous Et_2O. The combined crops of the product were recrystallized [*n*-hexane–C_6H_6 (10:1)] to give long, bright yellow needles (0.78 g, 4.53 mmol, 79%): mp 111–112°; ir (KBr) 1700 cm^{-1} (C=O) [lit.[17] 1701 cm^{-1} (Nujol)]; nmr ($CDCl_3$) δ 3.00 and 3.12 (2 s).

Anal. Calcd for $C_6H_{12}N_4O_2$: C, 41.85; H, 7.02; N, 32.54. Found: C, 41.76; H, 6.93; N, 32.84.

Azodicarboxyldipiperidide (**9**).—To a cooled solution of diethyl azodicarboxylate (**1**, 1.00 g, 5.74 mmol) in 30 ml of anhydrous Et_2O, piperidine (1.00 g, 11.74 mmol) was added dropwise with continuous stirring. The mixture was allowed to stand at 0° for 2 hr and the crystals which formed were filtered and washed with a small amount of Et_2O (anhydrous). The filtrate was concentrated to 8 ml and allowed to stand at 0° for 15 hr. The second crop of crystals was filtered and washed with a small amount of Et_2O (anhydrous). The combined product was recrystallized [*n*-hexane–C_6H_6 (10:1)] to give golden yellow crystals (0.92 g, 3.65 mmol, 64%): mp 135° (lit.[4] mp 134–135°); ir (KBr) 1705 cm^{-1} (C=O) [lit.[17] 1704 cm^{-1} (KBr)]; nmr (CCl_4) δ 3.15–3.77 (two partially overlapping broad peaks, 8 H, CH_2NCH_2), 1.47–1.88 (broad peak, 12 H, $CCH_2CH_2CH_2C$).

Anal. Calcd for $C_{12}H_{20}N_4O_2$: C, 57.14; H, 7.94; N, 22.22. Found: 57.12; H, 7.84; N, 22.14.

Diethyl 1,1-Dimethyltriazan-2,3-dicarboxylate (**4**).—This substance was prepared as by Diels and Paquin[3] and was recrystallized [*n*-hexane–C_6H_6 (15:1)]: mp 94–95° (lit. mp 92.5–93°,[3] 95°[3]); ir (KBr) 3260 (NH), 1760 (C=O), 1690 cm^{-1} (C=O); nmr ($CDCl_3$) δ 6.91 (broad peak, NH), 4.14 and 4.16 (2 q overlapping 8, J = 7.5 cps, 4 H, CO_2CH_2), 2.54 (s, 6 H, $N(CH_3)_2$], 1.30 (t, 6 H, CCH_3).

***N,N,N′,N′*-Tetramethylhydrazodicarboxamide** (**11**).—A solution of **8** (2.00 g, 11.61 mmol) in methanol (30 ml, anhydrous) was hydrogenated for 15 min at 50 psi using platinum oxide (20 mg) as a catalyst. After filtration and removal of the solvent, a white, crystalline residue was obtained which was purified by recrystallization (Me_2CO) to give colorless crystals (1.95 g, 11.20 mmol, 97%): mp 221° (lit.[18] mp 220–221°); ir (KBr) 3275 (NH), 1640 cm^{-1} (C=O); nmr ($CDCl_3$) δ 6.96 (broad peak, 2 H, NH), 2.93 [s, 12 H, $N(CH_3)_2$].

Hydrazodicarboxyldipiperidide (**10**).—A solution of azodicarboxyldipiperidide (**9**, 8.32 mmol) in piperidine (50 ml, anhydrous), was refluxed until the bright yellow color of the solution was completely discharged (2 hr). The mixture was taken to dryness and the white, crystalline residue obtained was purified by crystallization (CCl_4) to give colorless needles (1.90 g, 7.84 mmol, 94%): mp 180° (lit.[19] mp 179°); ir (KBr) 3275 (NH), 1645

TABLE III

Compd	Column[16] used	Temp, °C	Flow rate, ml/min	Retention time, min
Diethylmethylamine	III	60	7	6
Methylethylamine	III	95	5	9
Diethylamine	III	95	5	12.3
N-Methylpiperidine	I	85	20	8
Piperidine	I	90	15	9
Ethylpiperidine	I	90	15	13
Piperidine	I	90	15	9
Benzylpiperidine	II	150	90	10
Piperidine	I	90	15	9
Benzaldehyde	I	115	20	9
N,N-Dimethylbenzylamine	I	125	16	12
N-Methylbenzylamine	I	115	14	16
Benzaldehyde	I	115	14	11
N,N-Diethylbenzylamine	I	120	12	37
N-Ethylbenzylamine	I	120	12	25
Benzaldehyde	I	120	12	11
Dibenzyl ether	I	185	25	10.5
Benzaldehyde	I	135	15	4
Dibenzyl thioether	I	185	25	25
Benzaldehyde	I	135	15	4

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(16) Melting points were determined on a calibrated Thomas-Hoover capillary melting point apparatus and were corrected. Ir data were recorded on a Beckmann IR-8 spectrophotometer. Nmr data were recorded on a Varian Associates Model A-60 spectrophotometer using tetramethylsilane or 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as internal standard. Gas chromatographic data were obtained on an F & M Model 810-19, using a flame detector and columns packed with 12% w/w SE-30 (Wilkens Instrument and Research Inc.) on Chromosorb W, A. W., 60–80 mesh (Matheson Coleman and Bell) (4 ft × 0.25 in., column I), 12% Carbowax 20 M (Wilkens Instrument and Research Inc.) on Chromosorb W, A. W., 60–80 mesh (Matheson Coleman and Bell) (4 ft × 0.25 in., column II), and 40% Castorwax (Wilkens Instrument and Research, Inc.) plus 0.5% ATPEP-80 (Perkin-Elmer) on Chromosorb W, A. W. DMCS, 100–120 mesh (F & M) (10 ft × 0.125 in., column III) (Table III). Microanalyses were performed on an F & M 185 C, H, N analyzer Model 185 in this department.
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(18) R. J. Crawford and R. Raap, *J. Org. Chem.*, **28**, 2419 (1963).
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cm^{-1} (C=O); nmr ($CDCl_3$) δ 3.22–3.53 (m, 8 H, CH_2NCH_2), 1.38–1.70 (m, 12 H, $CCH_2CH_2CH_2C$). This compound was also obtained from **9** using the procedure outlined in the preparation of **11**.

Demethylation of *N*-Methylpiperidine (Preparative Method).—To a solution of *N*-methylpiperidine (2.48 g, 25.00 mmol) in C_6H_6 (20 ml, Na dry) was slowly added a solution of **1** (6.53 g, 37.50 mmol) in C_6H_6 (20 ml, Na dry) and the mixture was refluxed for 30 min.[20] The solvent and the unreacted *N*-methylpiperidine (0.25 g, 2.52 mmol, 10%) were removed under reduced pressure and the residue was dissolved in a mixture of 4 *N* HCl (25 ml) and EtOH (10 ml). The solution was refluxed for 2 hr and taken to dryness under reduced pressure. The residue was triturated with 10 *N* NaOH solution (1 ml) and extracted with Et_2O (3 × 25 ml). The combined extracts were dried ($MgSO_4$) and distilled to give piperidine (1.3 g, 15.27 mmol, 61%).

Diethyl *N*-(Piperidinomethyl)hydrazine-*N*,*N*′-dicarboxylate Hydrochloride (12).—To a solution of *N*-methylpiperidine (0.68 g, 6.84 mmol) in C_6H_6 (25 ml, Na dry) was added **1** (2.00 g, 11.48 mmol) and the mixture was allowed to stand for 24 hr at 25°. The mixture was filtered and the clear filtrate was taken to dryness under reduced pressure. The residue was dissolved in Et_2O (20 ml, anhydrous) and to the mixture was added a saturated solution of HCl in Et_2O (15 ml, anhydrous). The white precipitate which formed was filtered and dried over P_2O_5 and NaOH pellets under vacuum for 24 hr. The solid was triturated thoroughly with Me_2CO (5 ml, anhydrous) and the undissolved portion was filtered and washed twice with Me_2CO (1 ml, anhydrous). The residue (1.30 g, 4.20 mmol, 61%) was a white, microcrystalline powder: mp 162–163° dec; ir (KBr) 3200 (NH), 1750 (C=O), 1715 cm^{-1} (C=O); nmr ($CDCl_3$) δ 4.78 (broad pea, 2 H, $^+NCH_2N$), 4.23 and 4.26 (2 q overlapping, 4 H, J = 7.5 cps, CO_2CH_2), 1.30 (t, 6 H, CCH_3).

Anal. Calcd for $C_{12}H_{24}N_3O_4Cl$: C, 46.52; H, 7.81; N, 13.56. Found: C, 46.20; H, 7.69; N, 13.30.

A solution of **12** (0.25 g, 0.87 mmol) in 4 *N* HCl (10 ml) was refluxed for 2 hr and the mixture was distilled, leaving a white residue. The formaldehyde in the distillate was determined gravimetrically as its 2,4-dinitrophenylhydrazone.[8,21] The experiment was repeated after adding a known amount of 1% formaldehyde (3.00 ml, 1.00 mmol) to the solution of **12**. The concentration of formaldehyde was then estimated by comparing the results from the two experiments. After drying over P_2O_5 and NaOH pellets under vacuum, the white, crystalline residue was weighed and made into a homogeneous powder. A solution (10%) of small amount (40 mg) of the powder in CD_3OD was used for the nmr determination of piperidine hydrochloride (δ 1.80, m, 6 H, $CCH_2CH_2CH_2C$) and **6** (δ 1.22, t, 6 H, CCH_3). The overall analysis indicated that hydrolysis of **12** afforded equimolar amounts of formaldehyde, piperidine hydrochloride, and **6**.

Reaction of *O*-Acetyl Bulbocapnine with Diethyl Azodicarboxylate.—*O*-Acetyl bulbocapnine (**14**) (0.50 g, 1.36 mmol) was dissolved in 5 ml of absolute EtOH and the solution was added slowly to diethyl azodicarboxylate (0.50 g, 2.87 mmol) under N_2. The reaction mixture was allowed to stand for 12 hr; irregular yellow crystals (0.20 g) formed, were filtered, and were washed with 0.5 ml of absolute EtOH. A second crop of crystals was obtained by evaporating the solvent under reduced pressure and washing the residue several times with ether to obtain a pale yellow, amorphous powder (0.25 g). The product (**15**) was recrystallized (EtOH), purified over an Al_2O_3 column (Reagent, Merck) using $CHCl_3$ as an eluent, and recrystallized [absolute EtOH–EtOAc (1:1)] to give yellow crystals (0.41 g, 0.76 mmol, 56%): mp 179–182°; ir (KBr) 3250 (NH), 1705–1750 cm^{-1} (broad band, 3 C=O); nmr ($CDCl_3$) δ 6.02 (s, OCH_2O), 4.19 and 4.20 (2 overlapping 8, 4 H, $OCCH_2$–), 3.92 (s, OCH_3), 2.71 (s, NCH_3), 2.34 (s, $OCOCH_3$). The product was analyzed immediately after purification.

Anal. Calcd for $C_{27}H_{31}N_3O_9$: C, 59.88; H, 5.77; N, 7.76. Found: C, 59.73; H, 5.59; N, 7.40.

Preparation of Substituted Benzyldialkylamines.—To a mixture of a secondary amine (55.0 mmol) and 10 *N* NaOH solution was slowly added the appropriate benzoyl chloride (37.0 mmol). The addition required 1 hr and after an additional 1 hr of stirring, 10 *N* NaOH solution (3 ml) was added. After the heat subsided, the mixture was poured into ice–H_2O and the precipitate was collected.

$LiAlH_4$ (1.6 g, 42.0 mmol) was placed in 10 ml of Et_2O, and a solution of the amide (14.0 mmol) in Et_2O was added over 1.5 hr.

After refluxing for 2–12 hr and stirring for an additional 4 hr at 25°, the excess hydride was decomposed by the slow addition of H_2O (7 ml). The mixture was stirred for 1–3 hr and filtered, and the precipitate as washed several times with Et_2O. The filtrate and washings were dried ($CaSO_4$) and the Et_2O was removed.

The product was purified by dissolving it in 2 *N* HCl and extracting the solution with C_6H_6 (3 × 25 ml). The solution was then made basic with NaOH and again extracted with C_6H_6 (3 × 50 ml). The C_6H_6 extracts were dried ($CaSO_4$) and the C_6H_6 was removed.

Reaction of *N*-Benzylpiperidine with Azodicarboxylate Esters.—A mixture of *N*-benzylpiperidine (1.20 g, 6.84 mmol) and **1** (2.00 g, 11.48 mmol) in C_6H_6 (25 ml, Na dry) was refluxed for 6 hr and filtered, and the filtrate was evaporated to dryness under reduced pressure. After drying over P_2O_5 under vacuum for 12 hr, the residue was dissolved in Et_2O (20 ml, anhydrous) and to the mixture was added a saturated solution of HCl in Et_2O (15 ml, anhydrous). The white precipitate which formed was filtered and triturated thoroughly with Me_2CO (3 ml, anhydrous). The undissolved portion was filtered and washed with Me_2CO (0.5 ml, anhydrous). The residue (1.50 g, 3.89 mmol, 57%) was a white, hydroscopic, microcrystalline powder which was very labile in the presence of moisture.

A solution of the product (50 mg) in 0.1 ml of D_2O was allowed to stand for 2 hr, after which CD_3OD (0.5 ml) was added to the mixture. Nmr analysis of the resulting clear solution indicated the presence of equimolar amounts of piperidine hydrochloride (δ 1.80, m, 6 H, $CCH_2CH_2CH_2C$), benzaldehyde (δ 9.92, s, 1 H, CHO), and **6** (δ 1.22, t, 6 H, CCH_3).

Reaction of Azodicarboxylate Esters with Tertiary Amines. General Procedure.—To a solution of the tertiary amine (5.74 mmol) in C_6H_6 (29 ml, Fisher certified reagent over Na), the azodicarboxylate ester (11.48 mmol) was added and the mixture was refluxed until no increase was observed in the quantities of secondary amines, when the mixture was analyzed by the procedure.

Determination of the Unreacted Tertiary Amines.—The reaction mixture was transferred quantitatively into a 25-ml volumetric flask and diluted to the mark with C_6H_6 (anhydrous). Aliquots (5 μl) of this solution were injected into the glc and the integration corresponding to the peak of the tertiary amine was compared to that of a standard. The standard was prepared by making 25-ml solution of the tertiary amine (5.47 mmol) in anhydrous C_6H_6. Three readings were taken in each case and their averages were compared.

Determination of the Secondary Amines.—The reaction mixture was evaporated to dryness on a rotatory evaporator and the residue was dissolved in anhydrous C_6H_6 (20 ml). Dry HCl gas was bubbled into the solution for 15 min and the solvent was removed again on a rotatory evaporator. The residue was kept in a desiccator under vacuum (0.5 mm) over NaOH for 12 hr and then extracted thoroughly with distilled H_2O (50°). The extract was transferred quantitatively into a 20-ml volumetric flask and diluted to the mark with distilled H_2O. Aliquots (5 μl) of this solution plus aliquots (5 μl) of a 20% NaOH solution were injected together into the glc. The peak corresponding to the secondary amine was compared to that obtained by injecting an equal aliquot (5 μl) of a 20% NaOH hydroxide solution. The standard was prepared by making a 20-ml solution of the HCl salt of the secondary amine in distilled H_2O. Three readings were taken in each case and their averages were compared.

Determination of Benzaldehyde.—From the previous extract, aliquots (5 μl) plus aliquots (5 μl) of distilled H_2O were injected together into the glc. The peak corresponding to benzaldehyde was compared to that obtained by injecting an equal aliquot (5 μl) of the standard together with an aliquot (5 μl) of distilled H_2O. The standard was prepared by making a 20-ml solution of benzaldehyde in a H_2O–EtOH (2:1) mixture. Three readings were taken in each case and their averages were compared.

Debenzylation of Dibenzyl Ether (Preparative Method).—A mixture of dibenzyl ether (4.96 g, 25.00 mmol) and **1** (6.53 g, 37.50 mmol) was heated at 140° for 30 min. The reaction mixture was subsequently refluxed with H_2O (30 ml) for 1 hr and extracted with C_6H_6 (3 × 50 ml). The extracts were then dried

(20) Less reactive amines required longer refluxing time.

(21) M. Mouton, *Bull. Sci. Pharmacol.*, **46**, 148 (1939); *Chem. Abstr.*, **33**, 5128 (1939).

($MgSO_4$), the solvent was removed under reduced pressure, and the residue was fractionally distilled to give benzaldehyde (2.10 g, 19.79 mmol, 79%), benzyl alcohol (2.25 g, 20.80 mmol, 83%), and unreacted dibenzyl ether (0.55 g, 2.77 mmol, 11%).

Reaction of Dibenzyl Ether with Ethyl Azodicarboxylate.—A mixture of dibenzyl ether (1.14 g, 5.74 mmol) and **1** (1.00 g, 5.74 mmol) was heated at 140° for 30 min to give a colorless solid: ir (neat) 3280 (NH), 1740 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.36 (m, 10 H, aromatic), 6.48 (s, 1 H), 4.82 (m, 2 H, $OCH_2C_6H_5$), 4.25 and 4.27 (2 q overlapping, J = 7.5 cps, 4 H, CO_2CH_2), 1.27 (t, J = 7.5 cps, 6 H, CCH_3).

A small fraction of the product (50 mg) was refluxed with H_2O (0.2 ml) for 30 min and extracted with $CDCl_3$ (2 × 0.3 ml). Nmr analysis of the combined $CDCl_3$ extracts indicated that they contained equimolar amounts of benzaldehyde (δ 9.88, s, 1 H, CHO), benzyl alcohol (δ 4.60, s, 2 H, CH_2O), and **6** (δ 1.22, t, 6 H, $CCH_2CH_2CH_2$).

Reaction of Dibenzyl Thioether with Ethyl Azodicarboxylate.—A mixture of dibenzyl thioether (1.23 g, 5.74 mmol) and **1** (1.00 g, 5.74 mmol) was heated at 140° for 30 min to give a white solid mass: ir (neat) 3280 (NH), 1740 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.25 (m, 10 H, aromatic), 6.50 (s, 1 H), 3.92 (m, 2 H, $SCH_2C_6H_5$), 4.16 and 4.17 (2 q overlapping, J = 7.5 cps, 4 H, CO_2CH_2), 1.22 (t, J = 7.5 cps, 6 H, CCH_3). A small fraction of the product (50 mg) ws refluxed under N_2 with 1 N HCl (0.2 ml) for 1 hr and extracted with $CDCl_3$ (2 × 0.3 ml). Nmr analysis of the combined $CDCl_3$ extracts indicated that they contained equimolar amounts of benzaldehyde (δ 9.88, s, 1 H, CHO), benzyl mercaptan (δ 3.66, s, 2 H, CH_2S), and **6** (δ 1.22, t, 6 H, $CCH_2CH_2CH_2C$).

Determination of Unreacted Dibenzyl Ether or Dibenzyl Thioether by Glc.—A known amount (2.87 mmol) of the reaction mixture between **1** and the appropriate ether was transferred quantitatively into a 25-ml volumetric flask and diluted to the mark with a 1 N HCl solution in a H_2O–EtOH (1:1) mixture. The mixture was analyzed against a standard of the dibenzyl ether (2.87 mmol) or the dibenzyl thioether (2.87 mmol) following the same procedure as used in the determination of tertiary amines.

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Phosphorino[4,3-*d*]pyrimidines. III. Synthesis, Resolution, and Properties of 4-Substituted Phosphorino[4,3-*d*]pyrimidines[1]

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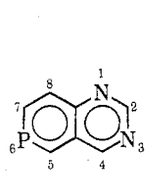
A family of 4-substituted 6-phenylphosphorino[4,3-*d*]pyrimidines has been prepared with 4-amino-1,2,5,6-tetrahydro-1-phenylphosphorin-3-carbonitrile as the key starting material. Pmr, ^{31}P nmr, infrared, and mass spectral data support the structures. Treatment of 4-amino-5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-*d*]-pyrimidine with benzyl bromide gave the corresponding phosphonium salt, which was resolved *via* its dibenzoyl tartrate salts. Ammonium bromide converted the diastereomers back to the enantiomeric bromides. Attempted methylation of 5,6,7,8-tetrahydro-6-phenylphosphorino[4,3-*d*]pyrimidine-4-thiol gave 5,6,7,8-tetrahydro-4-(methylthio)-6-phenylphosphorino[4,3-*d*]pyrimidine 6-sulfide *without* quaternization of the phosphorus atom. Spectral data for all of these compounds are briefly discussed.

Phosphorino[4,3-*d*]pyrimidines (**1**) represent a very recent[3] and intriguing family of compounds in the area



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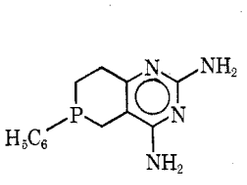

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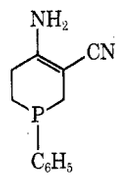

3

of fused carbon–phosphorus heterocycles. The 5,6,7,8-tetrahydro derivatives are prochiral about the asymmetric phosphorus atom, and 4-substituted pyrimidines, such as adenine and 6-mercaptopurine, are well known for their biological and medicinal value.[4] Recent evidence also indicates that quinazolines substituted at the 6 position, particularly heteroatom substituents, are of potential use as antimetabolites.[5] Additionally, C–P heterocycles which possess organic functionality are extremely rare in the literature[6,7] and hence very little is known of the biological activity conveyed by the phosphorus atom. The first reported[3] phosphorinopyrimidine was the 2,4-diamino derivative **2** prepared in a direct condensation of the 2-enamine nitrile **3** with guanidine. Interestingly, recent literature[8] suggests that a method of choice for the synthesis of 4-substituted fused pyrimidines involves the utilization of 2-enamino nitriles as their triethyl orthoformate adducts.

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