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SYNTHESIS AND PROPERTIES OF 1H-1,2,4-BENZOTRIAZEPINES[a]

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Abstract—The synthesis of some N,N-disubstituted benzhydrazidoyl chlorides and their reaction with cyano compounds in the presence of a Lewis acid are described. Whereas N-methyl-N-phenylbenzhydrazidoyl chloride (**1a**) gave 1*H*-1,2,4-triazoles, N,N-diphenylbenzhydrazidoyl chloride (**1b**) afforded 1*H*-1,2,4-benzotriazepines (**3b**) and N,N-(2,2'-biphenylen)benzhydrazidoyl chloride (**10**) yielded the corresponding 1*H*-1,2,4-benzotriazepine (**12**) or a hydrolysis product (**13**). Properties of compounds **3b**, specially their near-quantative acid hydrolysis to 1-phenylindazoles, are reported.

In order to synthesise new heterocyclic compounds with biological activity we investigated the synthesis of the hitherto unknown 1,2,4-benzotriazepine system.

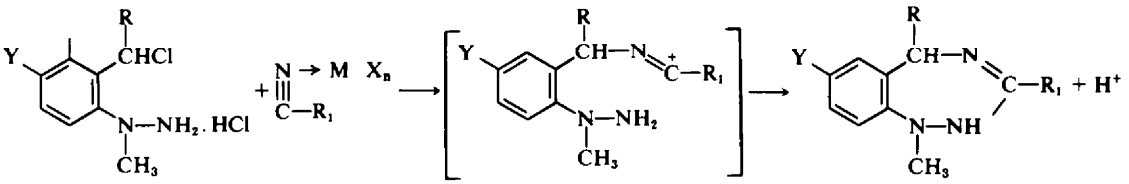
A first attempt (Scheme 1), based on our previously reported syntheses—via nitrilium salts—of dihydroquinazolines[1] and dihydrobenzodiazepines,[2] failed because of the instability of the required 2-chloromethyl-phenylhydrazine hydrochloride derivatives.[3]

In a second attempt (Scheme 2), inspired by Meerwein's quinazoline synthesis,[4] a benzhydrazidoyl chloride (**1**) should react with a cyano compound in the presence of a Lewis acid to give a nitrilium salt (**2**) whose carbocation should attack the ortho position of the benzene ring to yield, by intramolecular cyclisation, an 1*H*-1,2,4-benzotriazepine (**3**).

Three starting benzhydrazidoyl chlorides (**1a–c**) were selected in order to obtain three prototypes of 1*H*-1,2,4-benzotriazepines: 1-alkylated (**3a**), 1-arylated (**3b**) and 1-unsubstituted (via hydrolysis and decarboxylation of **3c**).

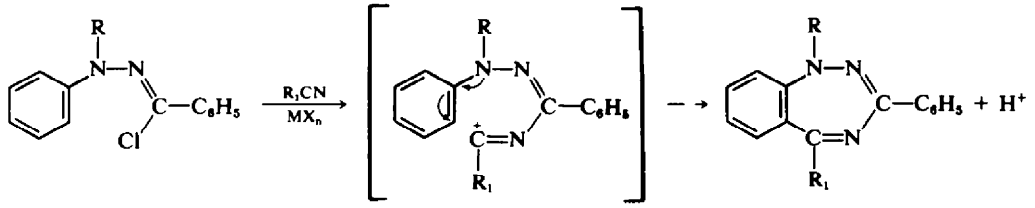
Compound **1a** was obtained in 83% yield by reacting equimolecular amounts of PCl_5 and N-methyl-N-phenylbenzhydrazide. To obtain **1b** in near quantitative yield, a molar ratio of N,N-diphenylbenzhydrazide:PCl_5 of 1:2 was necessary. Compound **1c** could not be obtained by this method because 2,4-diphenyl-1,3,4-oxidiazolone-5 (**4**) was produced in a side reaction.

*This paper is part 11 of our series on nitrilium salts. Part 10, *J. Med. Chem.* **15**, 887 (1972).



Y = R = H
Y = Cl, R = C_6H_5

SCHEME 1



1a, b, c **2a, b, c** **3a, b, c**

a: R = CH_3
b: R = C_6H_5
c: R = CO_2Et

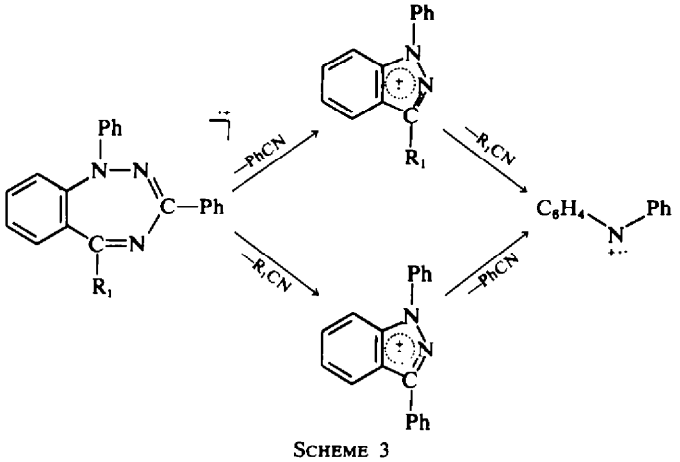
SCHEME 2

Compound **1a** did not react as expected with cyano compounds and instead of **3a**, 1*H*-1,2,4-triazoles were obtained. It is assumed that the carbocation of the intermediate nitrilium salt (**2a**) attacks the hydrazinic α-nitrogen, previously or not demethylated by the Lewis acid, to yield these compounds. Formation of the intermediate **2a** is shown by isolation of compound **5** after hydrolysis of the product of reaction of **1a**, benzonitrile and $AlCl_3$.

Compound **1b** did react with cyano compounds to afford in fairly good yield the 1*H*-1,2,4-benzotriazepines (**3b**, I-XIII) listed in the Table.

Compounds **3b** are coloured, colour intensity increasing with conjugation (compounds I–IV and XII are yellow, V–XI deep red). UV spectra appear to be characteristic (Table). IR spectra show an intense absorption band at 6·10–6·25 μ (C=N group). NMR spectra are consistent with the assigned structure, except compound **3b**-XII which shows that its structure must be **6**, derived from **3b**-XII by a prototropic change.

A general pattern of mass fragmentation of compounds **3b** is shown in Scheme 3.



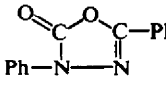
SCHEME 3

Compounds **3b** are stable to alkaline hydrolysis, but acid hydrolysis reveals a difference between 5-arylated- and 5-alkylated-**3b**. The former were slowly hydrolysed (Scheme IV) to the iminohydrazides **7** which, in turn, were hydrolysed even more slowly to 1-phenylindazoles (**8**) although a one-step, fast, near quantitative hydrolysis to **8** could be achieved with 70% H_2SO_4. On the other hand the 5-alkylated derivatives were rapidly hydrolysed to **8** and no **7** could be isolated. It must be pointed that iminohydrazides **7** are reconverted nearquantitatively to **3b** when heated in alcoholic KOH, this fact explaining the above mentioned stability of **3b** to alkalies.

From the above it would appear that synthesis of 1-arylindazoles from N′-aroyl-N,N-diphenylhydrazines represents an alternative method to the excellent one reported by Gladstone and Norman.[5]

Finally, the possibility of using N-aminoheterocycles to obtain tetracyclic 1*H*-1,2,4-triazepines was tried. N-benzoylaminocarbazole (**9**) reacted with PCl_5 (molar ratio 1:1) to yield 40% of the corresponding chloride **10**, the starting compound being recovered. In an attempt to get a better yield using a 1:2 molar ratio, a quantitative yield of compound **11** was obtained. Compound **11** was identified by direct comparison of its hydrolysis product, N-benzoylamino-3-chlorocarbazole, with an authentic sample prepared by an unequivocal synthesis.[1]

Compound **10** reacted with methylthiocyanate in the presence of $AlCl_3$ to yield 36% of the corresponding 1*H*-1,2,4-benzotriazepine **12**. This chloride, however, reacted with benzonitrile in the presence of $AlCl_3$ to yield **13**, a hydrolysis product of the expected benzotriazepine.



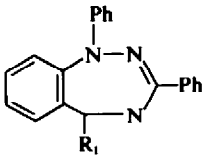
4

EXPERIMENTAL

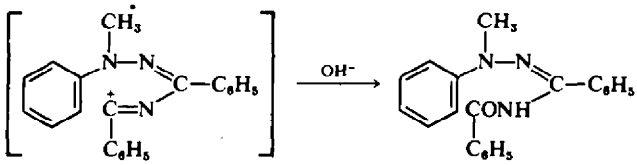
All m.ps are uncorrected and were taken on a Gallenkamp capillary m.p. apparatus. IR spectra were recorded on a Perkin-Elmer model 257 spectrophotometer. UV spectra were recorded on a Perkin-Elmer model 350 spectrophotometer. NMR spectra were taken on a Perkin-Elmer model R-12 spectrometer containing TMS as an internal standard. Mass spectra were taken on a Varian MAT-60 spectrometer.

N-Methyl-N-phenylbenzhydrazidoyl chloride (**1a**). A suspension of N-methyl-N-phenyl benzhydrazide[6] (30·3 g, 0·134 mol) and PCl_5 (30·0 g, 0·144 mol) in dry ether (75 ml) was stirred at room temp until a clear soln was obtained. The soln was poured into ice water and the ethereal layer was washed with ice water and dried ($MgSO_4$). The oil left by removal of the solvent was extracted with *n*-hexane in order to eliminate starting compound (2·9 g). The residue left by removal of *n*-hexane was a TLC pure yellow oil (27·4 g, 83%); λ_{max} (cyclohexane) 246 nm (ϵ 16,700), 290

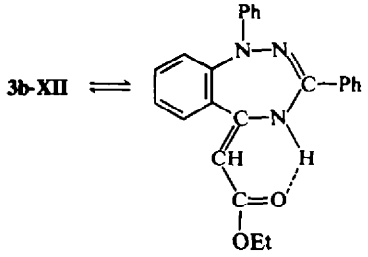
Table



Compound	R_1	Yield (%)	M.p. (solvent)	UV λ (nm)	UV $\epsilon \times 10^{-4}$	Formula	Elemental Analysis (calcd/found) % C	% H	% N
I	—S—Et	80	116–7 (EtOH)	253 278 (s)	2·93 1·98	$C_{22}H_{19}N_3S$	73·94 73·72	5·32 5·21	11·76 11·78
II	—S—Ph	55	149 (EtOH)	252 280 (s)	3·26 1·86	$C_{26}H_{19}N_3S$	77·03 76·87	4·69 4·66	10·37 10·11
III	—CH_2—CH_2—CH_3	80	100 (EtOH)	252 303 (s)	2·70 0·83	$C_{23}H_{21}N_3$	81·41 81·20	6·19 6·10	12·38 12·11
IV	—CH_2—CH_2—CH_2—CH_3	50	125 (EtOH)	252 302 (s)	2·63 0·86	$C_{24}H_{23}N_3$	81·55 81·22	6·51 6·81	11·88 11·53
V	—C_6H_5	70	214 (Pr^{n}OH)	253 267 (s) 315 (s)	2·77 2·55 0·93	$C_{26}H_{19}N_3$	83·84 83·71	5·09 5·26	11·26 11·40
VI	*p*-Me—C_6H_4	85	219–220 (Pr^{n}OH)	259 (s) 277 320 (s)	2·48 2·72 1·00	$C_{27}H_{21}N_3$	83·69 83·46	5·46 5·72	10·84 10·74
VII	*p*-Me—O—C_6H_4	57	155–6 (Pr^{n}OH)	250 (s) 303	2·04 2·56	$C_{27}H_{21}N_3O$	80·27 80·44	5·24 5·48	10·41 10·46
VIII	*o*-Cl—C_6H_4	62	195 (Pr^{n}OH)	251 262 (s) 315 (s)	2·52 2·36 0·90	$C_{26}H_{18}ClN_3$	76·58 77·00	4·41 4·61	10·30 10·52
IX	*m*-Cl—C_6H_4	55	140 (Pr^{n}OH)	251 320 (s)	2·82 0·93	$C_{26}H_{18}ClN_3$	76·58 76·75	4·41 4·49	10·30 10·27
X	*p*-Cl—C_6H_4	60	224–5 (Pr^{n}OH)	256 (s) 273 318 (s)	2·75 2·94 1·00	$C_{26}H_{18}ClN_3$	76·58 76·70	4·41 4·70	10·30 10·31
XI	*m*-O_2N—C_6H_4	60	214 (Pr^{n}OH)	245	4·01	$C_{26}H_{18}N_4O_2$	74·64 74·71	4·30 4·57	13·39 13·58
XII	—CH_2—COOEt	75	139 (EtOH)	241 314	3·10 2·51	$C_{24}H_{21}N_3O_2$	74·93 75·17	5·52 5·50	10·95 11·00



2a ($R_1 = C_6H_5$) 5



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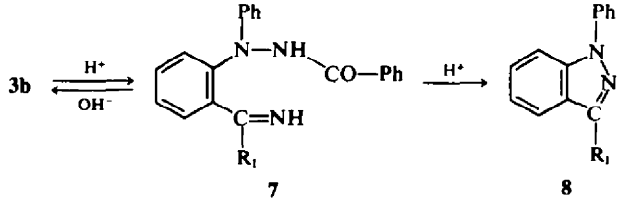
(3,200), 345 (6,100). IR ν_{max} 3090, 3060, 3030, 1580, 1560, 750, 685 cm^{-1}; NMR ($CDCl_3$) δ 3·38 (s, 3, CH_3), 6·9–8·2 (m, 10, ArH). (Found: C, 68·52; H, 5·43; N, 11·37. $C_{14}H_{13}ClN_2$ requires: C, 68·71; H, 5·31; N, 11·45%).

N,N-Diphenylbenzhydrazidoyl chloride (**2b**). A suspension of N,N-diphenylbenzhydrazide[7] (1·9 g, 0·066 mol) and PCl_5 (3·0 g, 0·0144 mol) in dry ether (50 ml) was refluxed with stirring until a clear soln was obtained. Proceeding in the same manner as in **1a**, a bright yellow solid (1·9 g, 94%) m.p. 97° was left on removal of the ether. Recrystallization from isopropanol (yellow plates) did not change the m.p.; λ_{max} (cyclohexane) 239 nm (ϵ 21,600), 289 (10,900), 347 (10,500); IR ν_{max} 3070, 3050, 1600, 1580, 760, 700, 693. (Found: C, 74·33; H, 5·00; N, 9·35. $C_{19}H_{15}ClN_2$ requires: C, 74·41; H, 4·89; N, 9·13%).

2,4-Diphenyl-1,3,4-oxdiazolone-5 (**4**). To a NaOEt soln, prepared from Na (1·3 g, 0·055 at. g) and abs EtOH (30 ml), β-benzoylphenylhydrazine (10·6 g, 0·05 mol) was added and the soln evaporated *in vacuo* to dryness. The residue, dry benzene (50 ml) and ethyl chloroformate (10·5 ml, 0·055 mol) were stirred at room temp for 2 hr. Water was added and the benzene layer dried (Na_2SO_4). Removal of benzene and recrystallization of the solid residue (12·4 g) from EtOAc afforded 8·4 g (59%) of N-phenyl-N-carboxyethylbenzhydrazide m.p. 132–134°; IR ν_{max} 3280, 1725, 1660, 1580, 1195. (Found: C, 67·32; H, 5·43; N, 9·72. $C_{16}H_{16}N_2O_3$ requires: C, 67·59; H, 5·67; N, 9·85%).

A suspension of the above compound (2·84 g, 0·01 mol) and PCl_5 (2·28 g, 0·011 mol) in dry ether (15 ml) was stir-



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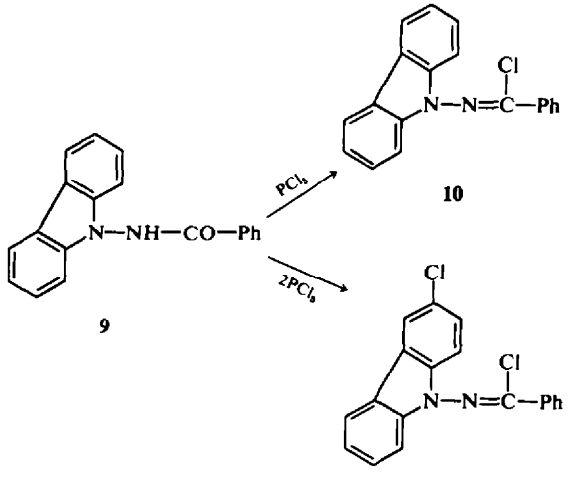
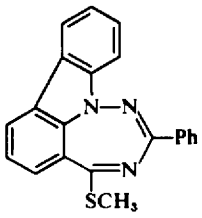


9 10 11



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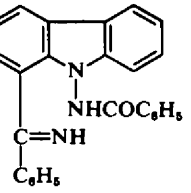

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red at room temp for 6 hr. The mixture was poured into ice water and the organic mixture, isolated in the usual manner, was chromatographed on a silica gel column. EtOAc–light petroleum (1:2) eluted 1·1 g (38%) of starting compound and 1·1 g of **4** as a colourless solid m.p. 113–114°, which recrystallized from ethanol with the same m.p. (Lit.[8] m.p. 113–114°).

1,3,5-*Triphenyl*-1H-1,2,4-*triazole*. A mixture of **1a** (1·2 g, 0·0049 mol), benzonitrile (5 ml) and $AlCl_3$ (0·76 g, 0·0056 mol) was heated at 120° for 30 min. The excess of benzonitrile was steam distilled from the basified mixture and the residue was chromatographed on preparative silica gel plates (EtOAc–light petroleum 1:5) to give many unidentified compounds and 0·51 g (35%) of the triazole m.p. 103–104° (Lit.[9] m.p. 103–104°).

1,3-*Diphenyl*-5-*methyl*-1H-1,2,4-*triazole*. A mixture of **1a** (1·2 g, 0·0049 mol), acetonitrile (5 ml) and $AlCl_3$ (0·76 g, 0·0056 mol) was refluxed for 4 hr. The cold mixture was basified with dil NaOH and extracted with EtOAc. From the residue of the solvent removal, 0·60 g (52%) of the triazole m.p. 95-96° (Lit.[9] m.p. 95–96°) were isolated by preparative chromatography as above.

N'-*Benzoyl*-N-*methyl*-N-*phenylbenzamidrazone* (**5**). A mixture of **1a** (4·9 g 0·02 mol), benzonitrile (10 ml) and $AlCl_3$ (2·7 g, 0·02 mol) was heated until the oil bath temp was 120°. The mixture was left to cool to room temp, basified with 20% NaOH and extracted with ether. Removal of ether and dilution of the residue with light petroleum left **5** (1·5 g) as a white solid m.p. 180° (isopropanol); IR ν_{max} 3280, 1647, 772, 758, 745, 692; NMR ($CDCl_3$) δ 3·28 (s, 3H, CH_3); 6·8–7·7 (m, 10H, NH and ArH). (Found: C, 76·41; H, 5·99; N, 12·64. $C_{21}H_{19}N_3O$ requires: C, 75·69; H, 5·77; N, 12·76%).

1H-1,2,4-*Benzotriazepines* (**3b**) (Table). General method. To a soln of **1b** (1·6 g, 0·0052 mol) and the cyano compound (0·006 mol) in dry *o*-dichlorobenzene, $AlCl_3$ (0·8 g, 0·006 mol) was added. An exothermic reaction set in and the mixture became deep red. The mixture was heated at 120–130° for 20 min, allowed to cool at room temp, basified with dil NaOH and extracted with ether. Solvents were steam distilled from the extract and the residue was subjected to column chromatography on silica gel employing EtOAc–light petroleum (1:10) to elute **3b**.

Hydrolysis of **3b**

With alcoholic KOH. After refluxing **3b**-VIII (0·5 g) in a soln of KOH (5 g) in EtOH (10 ml) and water (2 ml) for 48 hr, 0·42 g of **3b**-VIII were recovered.

With alcoholic HCl. (a) When a mixture of **3b**-VIII (0·4 g), EtOH (20 ml) and conc HCl (5 ml) was refluxed for about 1 hr, the colour changed from deep red to yellow and no **3b**-VIII could be detected by TLC. Evaporation *in vacuo* left 0·4 g (89%) of a yellow solid which after being washed with ether and recrystallized from ethanol–acetone had m.p. 228–229°. (Found: C, 67·32; H, 4·45; N, 9·37; Cl, 15·43. $C_{26}H_{20}ClN_3O{\cdot}HCl$ requires: C, 67·55; H, 4·55; N, 9·08; Cl, 15·38%). When this hydrochloride was treated with ether and dil NaOH, a solid (**7**, R = *o*-ClC_6H_4) was obtained which recrystallized from cyclohexane as yellow needles m.p. 168°; λ_{max} (ethanol) 247 nm (ϵ 23,500), 288 (14,000); IR ν_{max} 3475, 3310, 1657, 1628. (Found: C, 73·34; H, 4·70; N, 9·87; Cl, 8·32. $C_{26}H_{20}ClN_3O$ requires: C, 73·04; N, 4·94; N, 10·06; Cl, 8·24%).

(b) When a mixture of **3b**-V (0·78 g), EtOH (30 ml) and conc HCl (5 ml) was refluxed for 15 min the colour changed from deep red to yellow and no **3b**-V could be detected by TLC. Evaporation *in vacuo* left a yellow residue that was extracted several times with ether. Removal of ether afforded 0·18 g (32%) of 1,3-diphenyl-1*H*-indazole m.p. 101° (Lit.[3] m.p. 100–101°). The ether insoluble solid was treated with $CHCl_3$ and dil NaOH. Evaporation of the solvent left 0·50 g (62%) of **7** (R = C_6H_5) m.p. 179–180° (cyclohexane–EtOAc); λ_{max} (EtOH) 246 nm (ϵ 25,800), 292 (12,100); IR ν_{max} 3470, 3305, 1654, 1628. (Found: C, 79·91; H, 5·58; N, 10·86. $C_{26}H_{21}N_3O$ requires: C, 79·79; H, 5·37; N, 10·74%). When refluxing time was 5 hr the yield of **7** (R = C_6H_5) was 20% and yield of **8** (R = C_6H_5) was 67%.

(c) When **3b**-III was hydrolysed as in (b), it yielded after a few min 95% of 1-phenyl-3-propyl-1*H*-indazole b.p. 0·4 128°; n_D^{22} 1·618; λ_{max} (ethanol) 255 nm (ϵ 23,800), 306 (20,000); IR ν_{max} 2870, 2840, 2780, 1618; NMR ($CDCl_3$) δ 0·98 (t, 3H, CH_3), 1·88 (sext., 2H, CH_2), 2·98 (t, 2H, CH_2), 6·9–8·2 (m, 9H, ArH). (Found: C, 81·29; H, 6·71; N, 11·69. $C_{16}H_{16}N_2$ requires: C, 81·32; H, 6·82; N, 11·85%).

With 70% H_2SO_4. To 1·0 g of **3b**-V were added 20 ml of 70% H_2SO_4. The soln was heated for 45 min at 60°, then diluted with water (30 ml) and extracted with $CHCl_3$. From the extract were obtained 0·66 g (90%) of 1,3-diphenyl-1*H*-indazole.

1,3,5-*Triphenyl*-1H-1,2,4-*benzotriazepine* (**3b**-V). When a mixture of **7** (R = C_6H_5; 0·15 g), EtOH (10 ml), water (1 ml) and NaOH (0·2 g) was refluxed for about 30 min, 0·11 g of **3b**-V were obtained.

N,N-(2,2'-*Biphenylen*)*benzhydrazidoyl chloride* (**10**). A suspension of N-benzoylaminocarbazole[10] (10 g, 0·035 mol) and PCl_5 (8·1 g, 0·038 mol) in benzene–heptane 3:1 (130 ml) was refluxed for about 30 min. The soln was concentrated to 25 ml, absorbed on a silica gel column and eluted with EtOAc–light petroleum (1:10) to yield 4·18 g (40%) of **9** as a bright yellow solid m.p. 96–97° (*isopropanol*); λ_{max} (cyclohexane) 237 nm (ϵ 69,400), 288 (11,800), 287 (13,500), 292 (19,000), 380 (7,200); IR ν_{max} 3060, 1628, 1594, 748, 766, 685. (Found: C, 74·86; H, 4·19; N, 9·06; Cl, 11·90. $C_{19}H_{13}ClN_2$ requires: C, 74·90; H, 4·27; N, 9·19; Cl, 11·62%).

1,9-(o-*Phenylen*) -3- *phenyl* -5- methylmercapto-1H-1,2,4- *benzotriazepine* (**12**). A stirred mixture of **10** (0·67 g, 0·0022 mol), methylthiocyanate (3 ml) and $AlCl_3$ (0·35 g, 0·0025 mol) was heated at 100° for 1 hr. The cold mixture was treated with ice water and extracted with EtOAc. The extract was washed with water, dried ($MgSO_4$) and chromatographed on preparative silica gel plates, elution with EtOAc–light petroleum (1:20) yielded 0·27 g (36%) of **12** which recrystallized from isopropanol as dark red needles m.p. 127–128°; λ_{max} (cyclohexane) 240 nm (ϵ 43,700), 278 (39,000), 337 (8,900); IR ν_{max} 1620, 1570, 793; NMR ($CDCl_3$) δ 2·46 (s, 3H, CH_3), 6·6–7·8 (m, 10H, ArH), 7·8–8·2 (m, 2H, ArH). (Found: C, 73·59; H, 4·36; N, 12·09.

$C_{21}H_{15}N_3S$ requires: C, 73·88; H, 4·42; N, 12·30%).

1-Iminobenzyl-N-benzoylaminocarbazole (**13**). A mixture of **10** (1·0 g, 0·0033 mol), benzonitrile (5 ml) and $AlCl_3$ (0·51 g, 0·0038 mol) was heated at 105° for 5 hr. Excessive benzonitrile was steam distilled from the basified mixture and the residue was chromatographed on preparative silica gel plates to elute with EtOAc–light petroleum (1:5) 0·05 g of **10** and 0·55 g (47%) of **13** which recrystallized from EtOH as pale yellow needles m.p. 161°. (Found: C, 77·49; H, 5·86; N, 9·66. $C_{26}N_{19}N_3O \cdot C_2H_5OH$ requires: C, 77·21; H, 5·78; N, 9·64%).

A sample kept *in vacuo* at 90° for 24 hr lost the crystallization EtOH but maintained the m.p.; λ_{max} (EtOH) 236 nm (ϵ 32,300), 264 (15,300), 285 (7,800), 352 (2,600); IR ν_{max} 3470, 3370, 1633. (Found: C, 80·08; H, 4·96; N, 10·94. $C_{26}H_{19}N_3O$ requires: C, 80·10; H, 4·88; N, 10·77%).

The hydrochloride was obtained by treating an ethereal soln of **13** with ethereal HCl and had m.p. 232–240 (d) (EtOH–water).

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